SURGERY
Gynecology & Obstetrics
APRIL 1961
VOLUME 112
NUMBER 4

THE ETIOLOGY AND THERAPY OF ACUTE PYOGENIC PAROTITIS

JOHN S. SPRATT, JR., M.D., St. Louis, Missouri

THIS ARTICLE is presented for several reasons: (1) to review the history of acute bacterial parotitis at Barnes Hospital and Washington University Hospital from 1 January 1911 through 31 December 1959; (2) to compare the efficacy with which parotitis of various bacterial origins has been treated by different therapeutic methods; (3) to correct erroneous conclusions reached in a 1955 publication from Barnes Hospital entitled "Surgical Parotitis, a Vanishing Disease" (11); (4) to republish Byars' modification of Blair's description of a safe method for draining abscesses of the parotid gland; and (5) to compare the therapeutic results obtained in the treatment of Staphylococcus aureus parotitis at St. Louis City Hospital (Starkloff Memorial) and Barnes Hospital from 1 January 1952 to 3 December 1959 with the results obtained by Blair in several St. Louis hospitals from 1912 to 1923 using early surgical drainage as his sole therapeutic method.

MATERIAL

The data that serve as the basis of the discussion are derived from the review of 134 cases of parotitis coded in the Barnes and Washington University Hospital records between 1 January 1911 and 31 December 1959, from 19 cases of acute pyogenic parotitis occurring in St. Louis City Hospital (Starkloff Memorial) between 1 January 1952 and 31 December 1959, and from the personal series of 35 consecutive cases of acute pyogenic parotitis treated by Blair at various St. Louis hospitals from 1912 to 1923. Ten patients among the 35 cases in Blair's series and 10 among the 134 cases coded in the Barnes record file are duplications. Consequently, the total number of persons who are included in the present study is 178.

Among the 178 cases of parotitis 86 were of defined bacterial origin and 92 were undefined for various reasons subsequently discussed. This latter group of 92 cases of bacterially undefined pus-forming parotitis occurred in patients having a major primary medical or surgical disease and the parotitis was not attributable to parotid trauma, sialolithiasis, parotid neoplasm, uveoparotid fever, iodism, epidemic parotitis or any other clearly recognized cause of acute parotid swelling. The data from these cases are contained in Tables I to VIII and Figures 1 to 3 and serve as the basis for the following discussion.

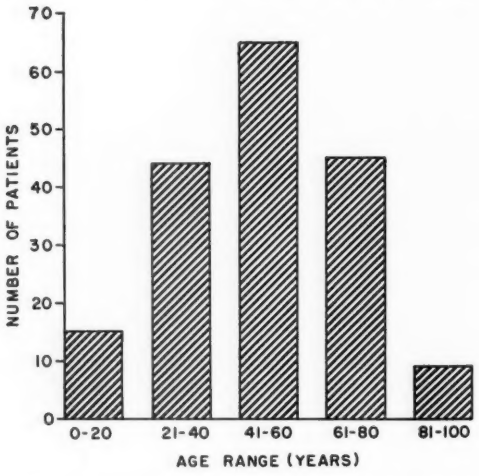


FIG. 1. Age distribution of 178 patients with acute pyogenic parotitis.

EVALUATION OF THE DATA

Consideration was given initially to the possibility that persons having parotitis might not be distributed randomly among the various causative bacteria and therapeutic methods. To eliminate a possible bias of patient distribution among various causative bacteria, the therapeutic methods were statistically compared only in cases of parotitis of uniform bacterial origin (Table I). Bias of the distribution of patients among the different therapeutic categories was evaluated by comparing the age distribution of patients in a therapeutic category with the age distribution of persons not treated by the same therapeutic method. The age distribution of all patients is contained in Figure 1 and the results of the distributional analysis are contained in Table II.

Antibiotics were used in the treatment of a group of older patients, and Blair treated a distinctly younger group (Table II). A very definite bias was found in the selection of patients for roentgen therapy since only 1 patient under 20 and only 1 patient over 80 years old were treated by this method. This observation suggests that roentgen therapy has been utilized only on the less ill and more co-operative patients and not for the extremely old or young.

By inspection of Table I other elements of bias are suggested. In every instance in the "no bacterial definition" group, the parotitis treated by any therapeutic method subsided without either septic complications or death of the patient from the parotitis. This observation suggests that many of the milder acute pyogenic forms of parotitis fall in this category. The persons who died without a culture of the terminal parotitis were mostly hopeless cases although 8 of these patients were probably salvageable and unquestionably died of the parotitis.

Another factor that precluded a complete analysis of therapeutic methods was the small number of cases in some of the bacterial categories (see Table I). For example, all 5 patients with pneumococcal parotitis recovered without difficulty regardless of the method of therapy. Parotitis caused by bacteria remaining highly susceptible to antibiotic therapy has been scarce in the antibiotic era. For example, only 2 patients having hemolytic streptococcal parotitis have been treated by antibiotics, and both of the infections subsided remarkably, whereas streptococcal parotitis in Blair's time was "of the greatest virulence clinically."

After the exclusion of the 31 patients in Table I considered to have died of a morbid

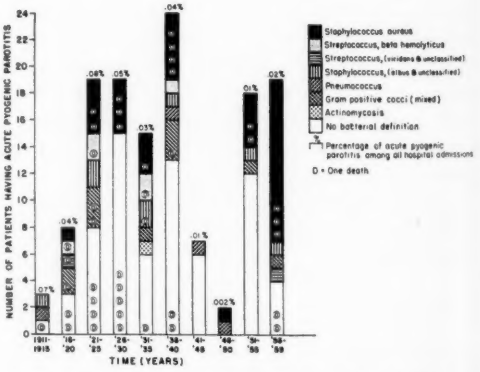


FIG. 2. Acute pyogenic parotitis occurring in 134 patients at Washington University and Barnes Hospitals 1911 through 1959.

illness other than parotitis no satisfactory system could be devised for determining whether the remaining patients with parotitis and the therapeutic methods were distributed at random among the numerous primary illnesses listed in Table III.

The completeness with which pyogenic parotitis was coded on the hospital records in the old Washington University Hospital (1911 to 1915) and in early years of Barnes Hospital is questioned. At least 17 of the 35 cases of acute pyogenic parotitis seen by Blair were from the Washington University and Barnes Hospitals. However, these cases were not identified by record number in Blair's article and in comparing the cases coded from the same hospital records from 1911 to 1923 with the published description of his 17 patients only 10 cases can be unequivocally cross-matched. Therefore, a significant number of cases of acute pyogenic parotitis occurring in association with another illness may not have been coded in the early years of the record system so that the true incidence of acute pyogenic parotitis in the early years of this hospital may have been higher than shown in Figure 2. The calculated incidence in recent years is correct because of the rigorous coding of all infections.

The parotitis was bilateral in 30 patients 8 of whom died. The gross mortality rate for bilateral parotitis and unilateral parotitis was the same ($P<.75$, $>.5$), and consequently the unilateral and bilateral infections have not been separated in the various statistical analyses.

INCIDENCE

The incidence of 134 cases of acute pyogenic parotitis coded on the records of 602,419 in-patients (excluding newborn infants) is represented in Figure 2. The impact that the routine use of antibiotics exerted upon the incidence and lethality of acute parotid infections between 1940 and 1950 is clearly demonstrated. The almost complete disappearance of this disease in surgical patients during this period led Robinson into the pitfall of labelling surgical parotitis, "a vanishing disease." The resurgence really did not begin until 1953 after he had completed his study. As Robinson indicated, sulfonamides and antibiotics were used almost routinely on the Barnes Surgical Service during this 1940 decade and the extreme efficacy of these drugs in preventing staphylococcal infections is supported by the complete absence of parotitis caused by Staphylococcus aureus in a postoperative patient from 1941 through 1952. However, true to Robinson's prediction the resurgence of parotid infections from antibiotic resistant Staphylococcus aureus with an accompanying gross mortality rate of 31 per cent from 1952 through 1959 has forced a re-evaluation of the management of parotid infections in general. Even since the resurgence has occurred acute pyogenic parotitis remains an infrequent disease developing in less than 2 out of every 10,000 hospital admissions and a long time (1911 through 1959) has been required to accumulate enough cases for statistically significant evaluation of only a portion of the various therapeutic methods that have been employed.

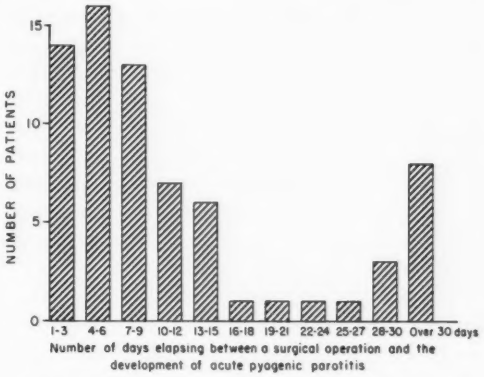


FIG. 3. Time elapsing between the performance of a surgical operation and the development of acute pyogenic parotitis in 71 patients.

ETIOLOGY

The spectra of pyogenic bacteria producing acute inflammations of the parotid gland are contained in Figure 2 and Table I.

These spectra have remained remarkably constant throughout all articles discussing the bacteriology of acute parotid infections since 1887, and appreciation of the propensity of acute parotid swellings to suppurate has been recognized at least since 1828 and possibly since the time of Hippocrates. Very infrequently has infection of the parotid gland been reported from bacteria other than gram positive cocci.

When acute pyogenic parotitis began to appear in postoperative patients in the early years of major abdominal surgery, much conjecture and speculation were recorded in an attempt to explain the origin of the fulminant lethal parotid infections. Retrograde ductal and hematogenous spread was recognized. The hematogenous infections were characterized by acute parotid swelling developing during or preceded by septicemia. Purulent ductal secretions were generally absent in these cases. These patients generally died and the parotid swelling was but an incidental terminal event.

Dehydration and a dirty mouth have been most incriminated as predisposing to the retrograde ductal infections. Dehydration was impossible to quantitate in a retrospective record review. However, many persons undoubtedly had a dehydrating illness (Table III), but many others had only a stressing primary illness without any evidence of dehydration.

Howard's recent observations again confirmed that salivary secretions can be abruptly arrested by either bodily injury or acute dehydration. In most cases the time of onset of acute pyogenic parotitis following major surgical procedures certainly coincided with the period of maximum stress (Fig. 3). Those patients with acute parotitis occurring more than 15 days after a surgical procedure had a terminal primary surgical illness (Fig. 3).

Those inflammations that subsided spontaneously usually did so within several days concurrently with the general improvement and hydration of the patient and the resumption of physiologic salivation. Stagnant salivation undoubtedly occurs frequently with many disorders but the coincidental association of stagnant salivary flow in the parotid duct and pyogenic gram positive coccal contamination of the duct was the combination that probably predisposed to most cases of pyogenic parotitis. The parotid gland and ducts are peculiarly susceptible to this invasion since the parotid is a serous gland and its stagnant ductal system contains no bacteriostatic mucus as do the ductal systems of the other mixed seromucous salivary glands. The reaction produced by the pyogenic contamination varied from mild parotid edema to fulminant massive edema with glandular necrosis, suppuration, and blood stream invasion. As will subsequently be discussed, the remarkably insignificant contribution that various therapeutic methods have had on the natural outcome of parotid infections caused by pyogenic bacteria other than Staphylococcus aureus (Table IV) suggests that some physiologic mechanism as the spontaneous resumption of parotid salivation is the most important factor in the subsidence of most cases of nonstaphylococcal parotitis. The milder forms of parotitis that subsided spontaneously usually did so in 2 to 3 days, the time period observed by Howard to be requisite for the spontaneous resumption of salivation in the acutely injured.

Numerous salivary stimulating agents as mouth washes, lemon juice, chewing gum, pilocarpine, and iodine have been used to hasten the return of salivation. However, no one has ever quantitated the restitution of salivary flow in an acutely inflamed parotid gland under the neurogenic suppression accompanying injury or dehydration to determine whether any of these agents hasten the return of flow which Howard observed would return physiologically with hydration and the passage of time. If the general improvement of the patient does not occur and if even relatively minor fluid deficits are not replaced soon after the onset of acute pyogenic parotitis, it is doubtful whether salivation will return spontaneously and the paro-

TABLE I.—THE DISTRIBUTION OF 178 CASES OF ACUTE PYOGENIC PAROTITIS ACCORDING TO THE METHOD OF THERAPY AND THE BACTERIAL ETIOLOGY (ST. LOUIS HOSPITALS, 1911 THROUGH 1959)

Therapeutic method	*Staphylococcus (aureus)* A	B	C	D	*Staphylococcus (albus and unclassified)* A	B	C	D	*Streptococcus (hemolytic)* A	B	C	D	*Streptococcus (viridans and unclassified)* A	B	C	D	*Pneumococcus* A	B	C	D	*Gram positive cocci (mixed infec.)* A	B	C	D	*Actinomycosis* A	B	C	D	*No bacterial definition* A	B	C	D	*Total* A	B	C	D
WASHINGTON UNIVERSITY HOSPITAL AND BARNES HOSPITAL (1911 THROUGH 1959)*																																				
No specific therapy			2	1	1						1	1					1				3		2						24		6	8	29		11	10
Roentgen therapy only		1																											4				4	1		
Roentgen therapy and antibiotics or sulfonamides	1	2	2	1																	1								4		2	5	3	2	3	
Antibiotics only				1													1												10			11			1	
Adequate early drainage only	5	1		1	2			1	1	1	1				1		1				3								5		1	17	2	2	3	
Drainage inadequate or delayed until patient moribund			4	1																														4	1	
Roentgen therapy and delayed drainage only	2			1	1	1											1												2			6	1		1	
Roentgen therapy, delayed drainage, and antibiotics or sulfonamides	2	3							1												1				1							3	5			
Drainage and antibiotics or sulfonamides	3				2								1								1								2			8		1		
Total	13	7	8	6	6	1		1	2	1	2	1	1		1		4				6	2	3		1				51		6	11	83	12	20	19
ST. LOUIS CITY HOSPITAL (#1) (1952 THROUGH 1959)																																				
No specific therapy																														1				1		
Roentgen therapy and antibiotics			1						1				1								1								3			5	1	1		
Antibiotics only																													2		2	2			2	
Roentgen therapy, delayed drainage, and antibiotics	2		1																													2		1		
Drainage and antibiotics	2		1																										1			3		1		
Total	4		3						1				1								1								6		1	2	12	1	4	2
BLAIR PERSONAL SERIES* 1912 TO 1923																																				
No specific therapy			1	1							3												1						6	1	1	4	6	1	3	8
Drainage only	5			1	3			1					1		1	1													3			1	13			4
Total	5		1	2	3			1			3	1			1	1							1						9	1	1	5	19	1	3	12

A, Parotid infection subsided without producing a septic complication or death.
B, Parotid infection subsided, but with a nonlethal septic complication.
C, Parotid infection or a directly attributable septic complication of the parotitis resulted in the death of the patient.
D, The parotid infection was superimposed upon an inevitably lethal primary illness, and the primary illness and not the parotitis was the cause of death.
*Ten cases in the Washington University-Barnes Hospital series and the Blair series are duplications.

titis may be expected to progress. On the day of onset direct observation of a number of the Stensen duct orifices in patients at the Barnes Hospital with the more fulminant form of staphylococcal parotitis disclosed no active salivation, and the duct had to be stripped to obtain only a few droplets of pus for bacterial culture.

The 92 cases of bacterially undefined parotitis should not be misconstrued as being "sterile." Every bacterial culture plated from the secretions and pus of the acutely inflamed parotid glands produced a growth of pyogenic cocci with the exception of 2 cases: one of these grew actinomycosis and from the second case a culture of pus was reported as showing "no growth," a report of doubtful validity. These 92 infections remained undefined for the simple reason that no culture was taken from the glands or their ducts. In only 2 case records were statements found to the effect that absolutely no ductal secretions could be obtained for culture excluding those cases of parotitis of probable

TABLE II.—ANALYSIS OF THE AGE DISTRIBUTION BETWEEN ALTERNATE THERAPEUTIC CATEGORIES OF PATIENTS HAVING ACUTE PYOGENIC PAROTITIS

Therapeutic method	*Probability that the age distribution of persons treated by method 1 is the same as the age distribution treated by method 2*	*Conclusion*
1. Drainage 2. No drainage	<.3, >.2	No significant difference in the age distribution in either category
1. Antibiotics or sulfonamides 2. No antibiotics or sulfonamides	<.001	Persons receiving antibiotics or sulfonamide therapy were significantly older
1. Roentgen therapy 2. No roentgen therapy	<.01	Subtesting established that neither the very young nor very old were treated by roentgen rays
1. Blair's patients 2. Remaining patients in study	<.001	Blair's patients were significantly younger
1. No specific therapy 2. Specific therapy	<.5, >.3	No significant difference in the age distribution in either category

hematogenous origin. In some of these cases of uncultured parotitis, stained smears of the ductal secretions were examined microscopically and gram positive cocci and leukocytes were invariably observed. In several instances cultures were not taken because of the hopelessness of an associated terminal illness. However, in most instances, failure to obtain a bacterial culture constitutes an indictment of our past attitude toward infections in general and acute pyogenic parotitis in particular.

THERAPEUTIC METHODS

The efficacy of the various methods employed in the treatment of bacterially defined parotitis was tested and the results are contained in Table IV. A standard chi square test of four square contingency tables containing the totals of all patients treated and the totals of all not treated by specific therapeutic methods (Table I) was utilized, and the null hypotheses tested are recorded at the foot of Table IV. The data in this table are quite interesting since they indicate that none of the therapeutic methods employed really influenced either the frequency of septic complications or the lethality of the infection with the single and highly significant exception of external surgical drainage for parotitis resulting from infection by Staphylococcus aureus. Table II quantitates the significance of age distribution in the different categories listed in Table V. The various therapeutic categories are discussed hereinafter.

NO SPECIFIC THERAPY

This nondescriptive category contains the cases of pyogenic parotitis treated by a variety of lesser methods not listed in Table I. None of the lesser therapeutic methods was employed in a sufficient number of cases to permit any statistical evaluation of their efficacy.

These lesser categories included hot packs, cold packs, massage, Stensen's duct cannulation and irrigation, dilatation of Stensen's duct, use of chewing gum, lemon drops, saturated solution of potassium iodide (systemically by mouth), pilocarpine, and, in some patients with terminal primary illnesses, no therapy at all.

Surprisingly, patients receiving no specific therapy but having a bacterially defined parotitis not produced by Staphylococcus aureus experienced no greater frequency of septic complications or death than did their counterparts treated by one of the major specific methods. Parotitis produced by Staphylococcus aureus apparently demanded some more vigorous therapy since only 5 patients having staphylococcal parotitis came in the "no specific therapy" category and all 5 died (Table I). It is conservatively estimated that at least 19 per cent of all cases of acute pyogenic parotitis not caused by Staphylococcus aureus subsided without complications or death after treatment consisting of nothing more than a mild salivary stimulant as chewing gum or lemon drops and a mouth wash.

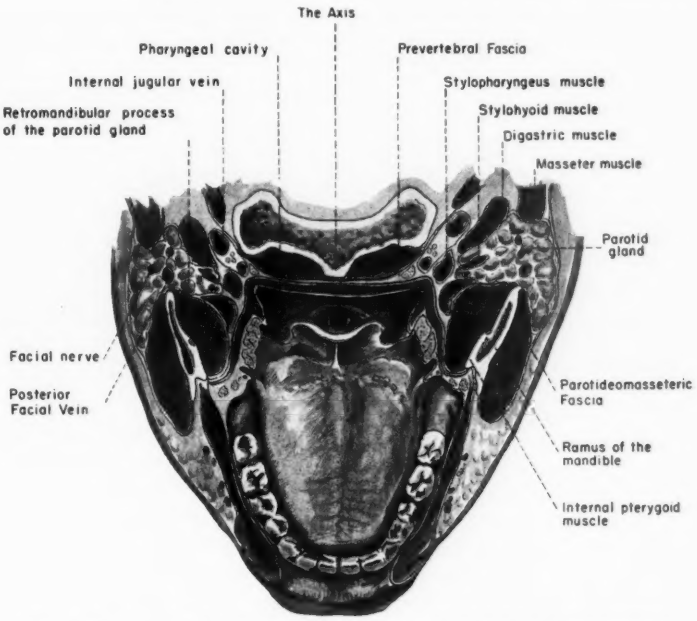


FIG. 4. The anatomic relations of the parotid gland (adapted from Toldt).

The use of large oral and parenteral doses of Lugol's solution for the treatment of acute pyogenic parotitis, as recommended by Leithauser and Cantor (9, 10) and by Altmeier could not be evaluated in the St. Louis series. These investigators concluded that Lugol's solution reduced the frequency of parotid suppuration. However, the gross mortality rate in Altmeier's series (15 of 49 patients, 30.6 per cent) was not significantly different ($P<.5, >.3$) from the gross mortality rate of the St. Louis series (7 of 31 patients, 22.5 per cent) for the same period of time (1936 through 1945). The use of Lugol's solution is based on the unproved assumption that iodine can stimulate edematous, acutely inflamed, nonsecreting parotid glands in acutely ill and dehydrated patients to salivate and that the resulting concentrations of iodine in parotid saliva are bactericidal to pyogenic cocci. Actually, the vehicle for the administration of the Lugol's solution used by both Leithauser and Altmeier was abundant amounts of oral water and parenteral saline, and control studies were not performed to determine whether the return of physiologic salivation that must accompany this vigorous rehydration would have accounted for the same favorable results without the Lugol's solution. Their rate of suppuration was still appreciable (Altmeier: of 46 patients treated with Lugol's solution suppuration had occured in 3 (6.5 per cent) before Lugol's solution was started; in 5 of the remaining 43 (11.6 per cent) suppuration occurred; in 6 of the 43 (13 per cent), the parotitis was unresolved at the time of death; and in 3 of 43 (7 per cent) the parotitis progressed during treatment with Lugol's solution and they were classified as "failures"). During the same decade (1936 through 1945), in 11 of 31 patients in the Barnes Hospital the parotitis was electively drained and a twelfth drained spontaneously. None of these patients received Lugol's solution, yet the gross surgical drainage rate at Barnes Hospital during this period does not differ significantly from the gross drainage and nonsubsidence in Altmeier's cases ($P>.9$). Among our 178 patients only 1 received

TABLE III.—ILLNESSES ASSOCIATED WITH ACUTE PYOGENIC PAROTITIS IN 178 CASES

Illnesses	*No.*	*Total No.*
Postoperative		71
Ophthalmologic	1	
Head and neck	4	
Dental	11	
Neurosurgical	3	
Thoracic	4	
Abdominal	23	
Anorectal	1	
Gynecologic	12	
Obstetric (infected abortion or full term delivery)	3	
Genitourinary	4	
Extremity and skeletal	5	
Untreated surgical illnesses		3
Terminal carcinomatosis		19
Primary pyogenic parotitis (generally in elderly people with dry mouths)		33
Neurologic		2
Psychiatric		4
Senility	1	
Psychosis	3	
Medical		46
Pneumonia	11	
Nephritis	8	
Hypertension	7	
Diabetes mellitus	5	
Leukemia or lymphoma	4	
Upper respiratory infection	3	
Pernicious anemia	2	
Typhoid fever	1	
Arteriosclerosis	1	
Hyperthyroidism	1	
Addison's disease	1	
Cellulitis	1	
Tuberculosis	1	
Grand total		178

Lugol's solution, and in this patient an extensive abscess developed producing a secondary osteomyelitis of the zygoma with sequestration of that bone.

If the neurogenic suppression of parotid glandular salivation in periods of stress and dehydration with coincidental pyogenic coccal ductal contamination is the pathogenesis of acute pyogenic parotitis, then it is certainly not surprising that such mechanical and physical measures as massage and ductal dilatation did not significantly improve the therapeutic results.

ANTIBIOTICS

Conclusions regarding the apparent inefficacy of antibiotics might be misleading were other factors not considered. In the first place patients receiving antibiotics were significantly older (Table II). Also from Figure 2 the frequency and lethality of pyogenic parotitis obviously were reduced drastically during the 1940 decade of almost routine antibiotic usage in postoperative patients, and consequently there is support for the conclusion that the antibiotics had value in preventing pyogenic parotitis. Since 1951, 16 of the 21 cases of bacterially defined pyogenic parotitis in Barnes Hospital were caused by a hemolytic Staphylococcus aureus resistant to penicillin and numerous other antibiotics. In 1 instance staphylococcal parotitis was treated from the day of onset with an antibiotic (erythromycin) to which subsequent examinations showed the causative staphylococcus to be sensitive. This inflammation subsided without suppuration of the gland or without septic complications. It should also be kept in mind that the present increase in the incidence of acute pyogenic parotitis is coincident with a drastic reduction in the use of routine antibiotics at this hospital. In fact only 5 of 22 patients having Staphylococcus aureus parotitis and only 5 of 33 patients having another type of parotitis were actually receiving or had recently received antibiotics at the onset of the parotitis between 1952 and 1959.

Since the advent of antibiotics, too few cases of pyogenic parotitis caused by bacteria sensitive to antibiotics have occurred to permit significant statistical evaluation of the efficacy of antibiotic therapy. The still occasional occurrence of acute pyogenic parotitis caused by bacteria highly sensitive to antibiotics, particularly beta hemolytic streptococcus, reiterates the importance of establishing accurate bacterial definition early in the course of any parotid infection.

EXTERNAL ROENTGEN THERAPY

The method of administration of roentgen therapy was identical in both Barnes Hospital and St. Louis City Hospital. Treatment was begun as soon as the patient was referred for roentgen therapy. Treatment consisted of 50 to 150 roentgens in air daily from a 200 or 250 kilovolt source through a lateral port large enough to cover the parotid gland and the edematous tissue about it.

TABLE IV.—COMPARISON OF THE INFLUENCE OF VARIOUS METHODS OF TREATMENT UPON THE SEPTIC COMPLICATIONS AND LETHALITY OF ACUTE PYOGENIC PAROTITIS

Therapeutic method	*Probability that null hypotheses A[1] and B[2] are acceptable[3]* — *Staphylococcus aureus parotitis*		*All other bacterially defined types of parotitis*	
	A	*B*	*A*	*B*
1. No specific therapy	No test (Only 3 persons in category 1, all dead)		<0.7, >0.5	<0.1, >0.05
2. Antibiotics, roentgen therapy or surgical drainage employed singly or in combination			Accept	Inconclusive[4]
1. Roentgen therapy	<0.1, >0.05	<0.5, >0.3	<0.7, >0.5	<0.5, >0.3
2. No roentgen therapy	Inconclusive[5]	Accept	Accept	Accept
1. Antibiotics	<0.5, >0.3	<0.7, >0.5	<0.95, >0.9	<0.5, >0.3
2. No antibiotics	Accept	Accept	Accept	Accept
1. External surgical drainage	<0.001	<0.02	<0.5, >0.3	<0.5, >0.3
2. No external surgical drainage	Reject[6]	Reject[6]	Accept	Accept
1. External surgical drainage established early	<0.001	<0.001	<0.5, >0.3	<0.9, >0.8
2. External surgical drainage delayed for roentgen therapy or until patient was moribund	Reject[6]	Reject[6]	Accept	Accept

[1]Hypothesis A: The frequency of septic complications attending the therapy of acute pyogenic parotitis by method 1 is the same as the frequency attending the therapy by method 2.
[2]Hypothesis B: The frequency of death from septic complications of the parotitis attending the therapy of acute pyogenic parotitis by method 1 is the same as the frequency attending the therapy by method 2.
[3]All cases in category D of Table I were excluded from the analyses.
[4]Trend for death to be more frequent with no specific therapy.
[5]Trend for septic complications to be more frequent with roentgen therapy.
[6]Significantly lower frequency of septic complications and death with external surgical drainage.

The daily treatments were given until the inflammation subsided or until a maximum cumulative dose of 400 to 600 roentgens (in air) had been administered. The lapse of time between the diagnosis of the parotitis and the administration of the first roentgen treatment was long (over 1 day) in most cases. However, all 4 patients with Staphylococcal aureus parotitis who received their first treatment on the day of diagnosis subsequently required external surgical drainage for suppuration.

On a careful review of all major articles considering the efficacy of radiation therapy against acute bacterial infections of the parotid gland, not one well controlled study can be found. As the responses to therapy tested (Table IV) indicate, any conclusions drawn from an uncontrolled study of the therapy of acute pyogenic parotitis would be meaningless.

In "Surgical Parotitis, a Vanishing Disease," the conclusion was made that the decrease in mortality attending the therapy of surgical parotitis dropped from 87.6 per cent in the 1921 through 1927 period to 33.33 per cent in the 1928 through 1937 period because of the introduction of radiation therapy of parotid infections. However, to quote Robinson, numerous other variables could have accounted for this decreased mortality rate: "The second group includes the years 1928 through 1937, and represents a period when much attention was being paid to aseptic intestinal anastomoses, fluid balance, and intestinal decompression by intubation during gastrointestinal surgical procedures. During the era the mortality rates attending colonic and gastric operations were greatly reduced." Furthermore, Robinson's study did not indicate that only 1 patient in the history of Barnes Hospital (see Table I) having Staphylococcus aureus parotitis was treated by roentgen therapy as the sole method of therapy. Most surviving patients treated initially by roentgen therapy have also required external parotid drainage. Gilchrist and McAndrew have also recently observed how frequently patients with staphylococcal parotitis require external drainage after roentgen therapy.

The effect of radiation on infections is still highly conjectural. Radiation was used in the therapy of practically every type of superficial and visceral infection between 1900 and 1940. However, by 1941, some of the more enthusiastic radiotherapists had conceded, as expressed by Ellinger: "We must unreservedly agree that operative measures in acute inflammations of deep seated organs should by

TABLE V.—COMPARISON OF THE INFLUENCE OF EXTERNAL DRAINAGE IN THE TREATMENT OF ACUTE STAPHYLOCOCCUS AUREUS PAROTITIS IN ST. LOUIS BETWEEN 1912 AND 1923 AND 1952 TO 1959

	Blair, St. Louis 1912 to 1923		*Barnes and St. Louis City Hospitals 1952 through 1959*	
	Drainage A	*Non-drainage B*	*Drainage C*	*Non-drainage D*
Subsided without septic complications	5	0	9	1
Subsided with septic complications	0	0	4*	1
Died with septic complications	0	1	2*	4
Died with other causes	1	1	0	1
Total	6	2	15	7

*Drainage delayed for the administration of roentgen therapy in 3 cases of parotitis that subsided with septic complications and 1 that produced death from septic complications.

HYPOTHESES TESTED:

1. The frequency of lethal and nonlethal septic complications is the same in group A as in group C: $P<.1, >.05$. Conclusion: Inconclusive, trend is for group A to have less complications.
2. The frequency of lethal and nonlethal septic complications is the same in group A as in group C less the 4 cases described in the footnote: $P<.5, >.3$. Conclusion: Accept.
3. The frequency of lethal and nonlethal septic complications is the same in group A as in group D: $P<.01$. Conclusion: Reject, group A has less complications.

Composite conclusion: From 1952 through 1959, acute Staphylococcal aureus parotitis treated by early drainage had the same low frequency of septic complications attained by Blair in the treatment by drainage only of acute Staphylococcus aureus parotitis in St. Louis from 1912 to 1923. The frequency of septic complications from 1952 through 1959 attending the therapy of Staphylococcal aureus parotitis by methods other than external drainage was significantly greater than the low frequency attained by Blair in the treatment of acute Staphylococcus aureus parotitis in St. Louis from 1912 to 1923.

no means be omitted in favor of roentgen therapy. The radiotherapy of inflammatory conditions is therefore an exceptionally heavy responsibility." Considering the anatomic situation of the parotid gland (see Fig. 4) astride the major vascular conduits to the brain, adjacent to the pharyngeal airway, and deep to a layer of unyielding fascia it is quite difficult to see how the parotid gland was not recognized as being a "deep seated organ." Very likely the relative infrequency of bacterial parotitis and the almost complete disappearance of the disease from 1941 to 1952 has permitted the continued survival of an empiric method of therapy. Certainly, the mean lethal dose of radiation for Staphylococcus aureus is well beyond tissue tolerance, and the effect of 600 roentgens (air dose) against virulent staphylococci deep in the parotid gland would be inconsequential. Also, the assumption that radiation significantly "dried up" or "stimulated" the parotid gland during an acute bacterial infection is completely erroneous with the exception that doses of radiation greater than 600 roentgens do produce a delayed reduction in the flow of saliva from a normal parotid gland after about 2 weeks. Within 2 weeks an acute pyogenic parotitis has either subsided, become chronic, killed the person, or required external drainage. Furthermore, the "drying up," even if it occurred rapidly, would detrimentally delay the restoration of physiologic salivation, and xerostoma is a definite late complication in mouths receiving over 600 roentgens.

Relief of pain following irradiation, if it occurred, was not measurable and it certainly was not dramatically abrupt. Suppuration and extension of the infection frequently occurred while time passed waiting for the "anti-inflammatory effect." As seen in Table I, only 1 of the 16 cases of Staphylococcus aureus parotitis treated initially by roentgen therapy subsided without septic complications, death, or subsequent drainage. This 1 patient also received massive doses of erythromycin, the drug to which the infecting strain of Staphylococcus aureus was highly sensitive. In short, the continued use of irradiation on acute bacterial infections of the parotid gland is a therapeutic anachronism.

EXTERNAL DRAINAGE

All the blame for delay in drainage cannot, however, be attributed to roentgen therapy. In several persons critically ill from parotitis, drainage of the parotid was postponed because fluctuation had not developed. Fluctuation was not observed in a single parotid gland containing a frank abscess in this entire study. The parotid gland is ensheathed in a dense capsule fixed by dense fibrous septa that separate the lobules of the gland (see Fig. 4). The tense, edematous, fixed capsule enclosing loculated pus does not permit the development of fluctuation as a sign of suppuration. Pitting edema of the facial skin does occasionally develop as a sign of underlying suppuration.

The importance of establishing external drainage for parotitis attributable to Staphylococcus aureus is quite significant (Table IV) An interesting comparison between results obtained in the preantibiotic era in St. Louis hospitals is contained in Table V. Delay in establishing indicated drainage led to a morbid progression of complications, except in those cases of parotitis in which laudable pus spontaneously formed a path for external drainage through the external auditory canal, the cheek, or rarely through the ductal system itself (Table VI).

External drainage as well as all other forms of therapy exerted surprisingly little influence on the natural history of parotitis caused by pyogenic bacteria other than the Staphylococcus aureus (Table V).

As indicated in Table VII, in very few cases was unnecessary surgical drainage performed. The objection raised by Leithauser and Cantor (9, 10) against the use of external drainage, namely the creation of a mixed infection by the surgical intervention, was never a problem. A transient facial nerve palsy developed in only 1 patient after external drainage, and this drainage was not performed by the technique of Byars. No external salivary fistulas persisted beyond the date of hospital discharge except in the 1 case of primary actinomycotic parotitis.

In brief, early external surgical drainage has been and remains the most consistently beneficial method of treating progressive acute pyogenic parotitis caused by Staphylococcus aureus.

COMPLICATIONS

The complications succeeding the development of acute pyogenic parotitis are tabulated in Tables VI and VIII. By inspection it is evident that many of these complications are attributable to unnecessary delay in establishing external drainage. Others arose from the nature of the infection. Only 2 complications could be classed as septic complications of drainage and both were erysipelas of the face following drainage of streptococcal parotitis.

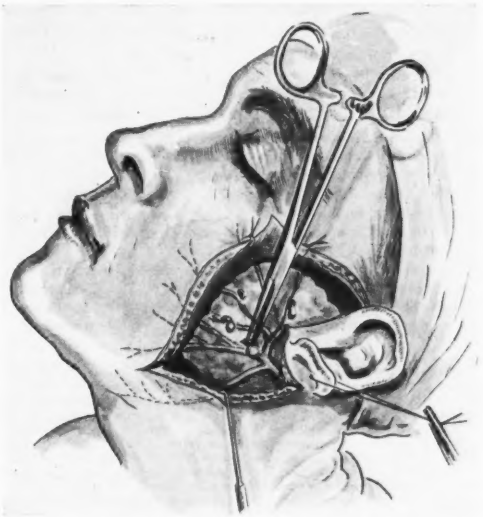


FIG. 5. Technique for the external surgical drainage of the parotid gland (adapted from Byars).

Three patients with parotitis treated initially by nondrainage had a relapse before dismissal from the hospital. Chronic pyogenic parotitis with indolent parotid abscesses chronically discharging pus through Stensen's duct is a late complication succeeding acute pyogenic parotitis (not surgically drained), but how frequently this late complication occurred could not be quantitated since few follow-up data after hospital discharge were available.

ANATOMY AND TECHNIQUE OF EXTERNAL DRAINAGE

Infections of numerous fascial spaces of the face and upper part of the neck may produce swelling and tenderness in the region of the parotid gland and may actually produce a secondary parotitis either by direct transgression of the infection into the parotid space or by lymphatic extension. Consequently, a comprehensive knowledge of all the fascial planes of the face and upper neck is essential to the surgical decompression of the parotid space. A detailed description of the fascial planes of the face and neck and of the surgical approaches to them for drainage

TABLE VI.—COMPLICATIONS ATTENDING INFECTIONS OF THE PAROTID GLAND WITH STAPHYLOCOCCUS AUREUS

Complications	*No. of patients having complications**	
	Nonlethal	*Lethal*
Spontaneous drainage of parotid abscess into external auditory canal	2	
Extension of parotid abscess into neck	1	
Osteomyelitis of the cervical spine	1	
Staphylococcal empyema	1	
Staphylococcal infection of an abdominal wound	1	
Relapse of the parotitis	1	
Septicemia with shock		7†
Massive swelling		4
Acute staphylococcal pyelonephritis		1
Total	7	12

*Patients are tabulated by the most serious complication succeeding the development of staphylococcal parotitis. Many patients actually suffered multiple complications of their staphylococcal infections. See Table VIII.

†Of all the patients dying with undrained parotitis, the pathologic prosector opened the parotid gland at necropsy in only 1 patient. This parotid gland contained a massive abscess. Shortly before death a note in the clinical record stated: "No fluctuation, no indication for drainage." This patient died of staphylococcal septicemia. How many other patients died of septicemia originating from an undrained abscess will never be known.

TABLE VII.—OBSERVATIONS ON THE STATUS OF 61 PAROTID GLANDS AT THE TIME OF EXTERNAL SURGICAL DRAINAGE FOR ACUTE PYOGENIC PAROTITIS

Status of gland	*Type of acute pyogenic parotitis*		
	Bacterial defined		
	Staphylococcus aureus	*(not Staphylococcus aureus)*	*No bacterial definition*
Pus present	17	13	8
Glandular necrosis	3	3	
Glandular edema	3	4	1
No description in operative note	6	0	2
Total	29	20	11

is contained in the work of Coller and Yglesias and of Casberg.

Our particular concern is with the parotid space formed by the superficial layer of the deep cervical fascia. This fascia splits at the inferior margin of the parotid gland into a superficial layer attaching superiorly to the zygoma and a deep layer continuous with the stylomaxillary ligament. The only weakness in this fascial capsule lies between the styloid process and internal pterygoid muscle. Medial to this weakness is the loose areolar tissue of the lateral pharyngeal space extending superiorly to the base of the skull and inferiorly into the mediastinum. Respiratory obstruction can be produced either by rupture of a parotid abscess into the lateral pharyngeal space or by edema of the pharynx and larynx secondary to the massive edema that can accompany any acute pyogenic parotitis.

The superficial layer of the parotid fascia is a thick unyielding cover and it is infrequent that a parotid abscess will spontaneously drain through the cheek although it occasionally does by secondary necrosis of the overlying skin and fascia. More frequently the superficial route of spontaneous parotid drainage is through the thin floor of the external auditory canal.

The anatomic juxtaposition of the parotid space to many other important anatomic structures of the upper neck (Fig. 4) accounts for many of the complications secondary to pyogenic parotitis observed in our patients such as septic arthritis of the temporomandibular joint, osteomyelitis of the zygoma, osteomyelitis of the mandible, septic thrombosis of the jugular vein, pharyngeal and laryngeal obstruction and edema, and the extension of parotid abscesses to other anatomic spaces of the temporal region, face, and neck.

Drainage of the parotid space is most safely effected by Byars' modification of Blair's technique (2, 3) as condensed in Figure 5. The cutaneous incision begins at the junction of the helix with the temporal skin and extends inferiorly just anterior to the ear, curving posteriorly below the lobule of the ear and around the angle of the mandible anteriorly along the inferior margin of the mandible for several centimeters, always following the natural cutaneous lines. The incision extends in depth to the superficial parotid capsule. Subcutaneous flaps are elevated both anteriorly and posteriorly until the entire superficial surface of the parotid gland is visible. Then, a small blunt clamp is used to perforate the multiloculated parotid abscess at many points. At each puncture the jaws of the clamp are spread gently in the direction of the facial nerve branches. An assistant whose sole function is to observe the face announces promptly any twitching of the facial muscles appearing at the time the capsule is punctured and the jaws of the clamp are

spread. If twitching occurs, the clamp is withdrawn from the focus of stimulation. To attempt sharp incisional drainage of the multiple parotid loculations risks the transection of the facial nerve branches since the direction taken through the parotid gland by these fibers is not predictable. Drainage of the deep portion of the gland is effected by elevating the lower pole of the parotid. By guarding the external jugular vein and staying anterior to the external carotid artery the dissection is extended deeply to the deep pole of the parotid gland and the lateral pharyngeal space. The deep lobules of the parotid are bluntly opened in the same manner as was used on the superficial lobules. Without this deep dissection, a critical portion of the gland will not be adequately drained. The incision is then held open by a light pack changed frequently according to the quantity of drainage. After purulent drainage has ceased the large wound will close without sutures and with negligible scarring.

The cutaneous incision and hemostasis and the elevation of the cutaneous flaps may be performed painlessly under the subcutaneous infiltration of the skin of the cheek and the blockage of the greater auricular nerve with local anesthesia. After the parotid is visible and before the multiple deep punctures are made a light general anesthesia may be given to those patients who will tolerate the anesthesia. If the general anesthesia cannot be tolerated, the multiple deep punctures may also be made under local anesthesia with minimal discomfort. Drainage should always be undertaken in the operating room with proper equipment and assistants and should never be undertaken in the ward.

TABLE VIII.—COMPLICATIONS SUCCEEDING THE DEVELOPMENT OF ACUTE PYOGENIC PAROTITIS AMONG 178 PATIENTS

Complications	*No. of times complication observed*
Respiratory obstruction (clinical signs)	13
Septicemia (proved by blood culture)	12
Septicemia (suspected, but no blood culture taken)	7
Pneumonia	5
Spontaneous drainage of parotid abscess through external auditory canal	5
Massive, lethal swelling of face and upper neck	4
Lung abscesses (proved by necropsy or drainage)	4
Metastatic abscesses to kidneys	3
Relapse of parotitis (treated initially by nondrainage)	3
Extension of parotid abscess into neck	2
Erysipelas of face (after drainage of streptococcal parotitis)	2
Glottic edema (necropsy proved)	2
Osteomyelitis	
Mandible	2
Zygoma	2
Cervical spine	1
Acute glomerulonephritis following beta hemolytic streptococcal parotitis	1
Extension of parotid abscess into subtemporal space	1
Spontaneous drainage of parotid abscess through sloughed cheek	1
Surgical wound infection by same bacterium causing parotitis	1
Jugular vein thrombosis (necropsy proved)	1
Necrotizing pharyngitis	1
Meningitis	1
Trismus and pain	Universally present, severity was directly related to the extent and acuteness of the parotid swelling

RECOMMENDED THERAPY

A plan of therapy encompassing our various observations might be summarized as follows:

1. As soon as the diagnosis of parotitis is made, exudate from Stensen's duct is obtained for a stained smear, a bacterial culture, and the determination of the antimicrobial drug sensitivities of the infecting bacteria. If no exudate is obtainable, the duct should be cannulated gently with a small polyethylene catheter and irrigated to obtain material for culture. A blood culture should be obtained.

2. Initial antimicrobial therapy should be directed toward resistant strains of gram positive cocci, particularly Staphylococcus aureus. As soon as antimicrobial drug sensitivity studies are available on the bacteriologic culture, specific antibiotics should be administered.

3. Restoration of a normal blood volume and a normal state of hydration and allevi-

ation of the primary illness should be effected expeditiously.

4. Frequent use of antiseptic mouth wash, mechanical cleansing of the teeth, and salivary stimulants will improve the oral hygiene and may accelerate the rate of salivation after physiologic salivation returns and should therefore be used. (It has not been shown that these agents will hasten the return of physiologic salivation in a dehydrated or severely ill patient.)

5. The specific indications for surgical drainage may be divided into early and late:

Early.—The very rapid progression of the parotitis with a rapidly rising white blood cell count and fever and the rapid deterioration of the patient are the prime indications for early drainage. Early drainage should be effected before the edema has progressed to the point that the airway may be obstructed or that painful trismus prevents adequate alimentation. Pain, poorly tolerated by the very ill and elderly, may be of such intense severity that early decompression of the parotid space is required for its relief. Do not wait for fluctuation.

Late.—The unequivocal indications for late drainage are as follows: (a) progression of edema to the point that the airway is in danger of obstruction from external pharyngeal pressure and glottic edema; (b) progression of edema, trismus, and pain to the point that oral alimentation is impaired; (c) the continued spread of pyogenic infections to other parts of the body from a chronic parotid abscess; (d) spontaneous drainage (always an inadequate drainage) of a parotid abscess; (e) continued presence of a parotid mass, pain, and fever after adequate antimicrobial therapy and hydration; (f) extension of a parotid abscess into other fascial spaces of the face and upper neck (The surgical approaches for drainage of all potentially infective fascial spaces of the temporal region, face, and neck are described by Coller and Yglesias and Casberg); (g) the percutaneous aspiration of intraglandular pus; (h) causation of progressive or nonresolving parotitis by an antibiotic resistant strain of hemolytic, coagulase positive Staphylococcus aureus.

6. The external drainage should be performed by exposing the entire superficial surface of the parotid gland and by making multiple spreading punctures with a small clamp into the many loculations of the gland including the deep portion of the gland behind the mandible. The facial nerve is protected by spreading the introduced clamp approximately in the direction of the nerve fibers and by not spreading the clamp at all in areas in which stimulation of the clamp produces facial twitching.

7. If fever and sepsis persist after drainage suspect, search for, and treat (a) undrained loculations of pus in the gland, (b) septicemia, (c) hematogenous metastasis of the infection to other organs, (d) direct extension of the pyogenic infection to adjacent spaces and structures of the face and neck, and (e) the development of pyogenic pneumonia or empyema.

8. When respiratory obstruction is not relieved by external drainage suspect the presence of pharyngeal or glottic edema or pneumonia. A tracheostomy is occasionally required.

9. When trismus persists after adequate external drainage look for septic involvement of the temporomandibular joint or osteomyelitis of the mandible.

10. When the drainage of pus from a parotid incision continues for prolonged periods of time suspect a secondary osteomyelitis, inadequate drainage of a portion of the parotid abscess, distal obstruction of Stensen's duct (stone or stricture), or a granulomatous infection.

SUMMARY

The case histories of 178 patients treated for acute pyogenic parotitis in St. Louis hospitals between 1911 and 1959 have been reviewed. Analyses of the results of different methods of treatment used during these 49 years indicated that the septic complications and lethality have been remarkably little

influenced by the therapeutic methods employed. The one highly significant exception was external drainage for pyogenic parotitis caused by Staphylococcus aureus. The utilization of adequate external drainage for staphylococcal parotitis was attended by a significant reduction in septic complications and lethality.

The argument has been presented that acute pyogenic parotitis results when Stensen's duct is coincidentally contaminated with a pyogenic gram positive coccus during a period when parotid salivation is depressed by dehydration or a severe primary illness. The reaction produced by the contaminating bacteria varies from mild transient edema to massive edema with glandular necrosis, suppuration, and blood stream invasion. At the present time, the more fulminant invasion occurs with antibiotic resistant Staphylococcus aureus, and early surgical decompression of the parotid space is generally necessary to prevent the progression of the bacterial invasion. Milder cases of acute pyogenic parotitis may be expected to subside with specific antibiotic therapy and the return of physiologic salivation.

REFERENCES

1. ALTMEIER, W. A. Acute secondary parotitis. Surgery, 1946, 20: 191–199.
2. BLAIR, V. P., and PADGETT, E. C. Pyogenic infection of the parotid glands and ducts. Arch. Surg., 1923, 7: 1–36.
3. BYARS, L. T. Preservation of the facial nerve in operations for benign conditions of the parotid area. Ann. Surg., 1952, 136: 412–421.
4. CASBERG, M. A. The clinical significance of the cervical fascial planes. Surg. Clin. N. America, 1950, 30: 1415–1434.
5. COLLER, F. A., and YGLESIAS, L. Infections of the lip and face. Surg. Gyn. Obst., 1935, 60: 277–290.
6. ELLINGER, F. The biologic fundamentals of radiation therapy. Chap. 17—The effects upon inflammation. New York: Elsevier Publishing Co., Inc., 1941.
7. GILCHRIST, R. K., and MCANDREW, J. R. Surgical parotitis. Arch. Surg., 1958, 76: 863–867.
8. HOWARD, J. M. Gastric and salivary secretion following injury; the systemic response to injury. Ann. Surg., 1955, 141: 342–346.
9. LEITHAUSER, D. J., and CANTOR, M. O. Lugol's solution in acute secondary parotitis. Ann. Surg., 1935, 101: 1171–1174.
10. Idem. Massive doses of Lugol's solution in acute secondary parotitis. Ann. Surg., 1940, 111: 650–654.
11. ROBINSON, J. R. Surgical parotitis, a vanishing disease. Surgery, 1955, 38: 703–707.
12. TOLDT, C. An Atlas of Human Anatomy. Vol. II, p. 415. New York: The Macmillan Co., 1928.

INFLAMMATORY CARCINOMA OF THE BREAST

KENT W. BARBER, JR., M.D., MALCOLM B. DOCKERTY, M.D., and
O. THERON CLAGETT, M.D., F.A.C.S., Rochester, Minnesota

In 1924, Lee and Tannenbaum described 28 cases of inflammatory carcinoma of the breast and, thus, firmly established as a clinical entity this uncommon, interesting, and highly malignant form of mammary carcinoma. Subsequent publications by Taylor and Meltzer in 1938, Meyer and associates in 1948, Chris in 1950, and Haagensen in 1956 have contributed to a better understanding of the clinical and pathologic features peculiar to this condition.

In the literature, there has been a recent resurgence of interest concerning the form of therapy to be employed for patients thus affected. The attitude has varied from a nihilistic one as advocated by Treves, which implies that a diagnosis of inflammatory carcinoma means categorical inoperability, to a more positive one as advocated by Fitts, which places emphasis on a bold surgical attack on most of the primary lesions. We, therefore, believe it pertinent to review at this time our most recent experience with inflammatory carcinoma of the breast as observed at the Mayo Clinic.

MATERIAL AND METHOD

The records of approximately 3,200 consecutive patients with malignant lesions of the breast who were encountered at the Clinic from 1946 through 1956 were reviewed. Those lesions which exhibited inflammatory signs, such as redness and edema, were selected for further study. We realize that the incidence of inflammatory carcinoma in any reported series of cases varies with liberality of the diagnostic criteria established by the examiner. We accepted the criteria of Haagensen as a basis for "certifying" the eligibility of our cases. These included enlargement of the breast accompanied by both redness and edema, each involving more than a third of the mammary area. After exclusion of those cases in which redness and edema represented local evidence of a cutaneous inflammatory reaction at the site of skin attachment of the tumor, 53 cases were left for study.

Primary therapy had consisted of radical mastectomy with postoperative irradiation in 42 patients, radical mastectomy alone in 6, simple mastectomy in 2, and biopsy and irradiation therapy in 3. Two of the 4 patients with bilateral, simultaneous disease had bilateral radical mastectomies, 1 patient had bilateral simple mastectomy, and the fourth had biopsy with irradiation therapy. There were no postoperative deaths.

Preserved gross specimens were available in all instances. When necessary, additional blocks of tissue were cut for paraffin embedding and sectioning.

OBSERVATIONS

The incidence of inflammatory carcinoma was 1.7 per cent in the series of approximately 3,200 patients with malignant lesions of the breast. The mean age of the patients, all women, was 52.3 years, the extremes being 25 and 78 years. Thirty-four of the patients were parous, but in only 1 patient did the carcinoma occur during pregnancy and lactation. On initial examination, the right breast alone was involved in 27 patients, the left alone in 22, and both in 4. Subsequently, 11 patients had involvement of the other breast, 10 by metastasis and 1 by development of a noninflammatory primary carcinoma.

Symptoms. The presence of a mass and pain, swelling, and redness were the commonest symptoms and were observed by the

From the Sections of Surgical Pathology and Surgery, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

patients in approximately 68, 62, 49, and 45 per cent of cases, respectively. Retraction of the nipple, enlargement of the axillary nodes, mammary pruritus, warmth, and soreness of the arm were less commonly observed in about 17, 13, 6, 6, and 2 per cent, respectively. The mean preoperative duration of symptoms was 2.9 months.

Signs. So closely did the condition in some patients resemble that of an infectious process that it was erroneously diagnosed and treated as such in 13. In accordance with the criteria of selection, the skin overlying the lesions in all 53 patients was red and edematous. A diffusely enlarging mass was present in 33 patients, while the remainder had more localized, smaller swellings. For the most part, these lesions were centrally placed with respect to the nipple. The reddened skin in 11 patients was recorded as being distinctly warm to palpation, and we are confident that the recorded incidence would have been higher had the various examiners been more conscious of this important sign.

Palpably enlarged axillary nodes were a constant feature in all 53 patients, and 6 patients had enlargement of supraclavicular lymph nodes as well. Fixation of the tumor to the skin was not a common finding, as a consequence of the edema present; in 17 patients, however, there was retraction of the nipples.

Pathologic findings. Grossly, the skin of the breasts containing the primary lesion was, in general, thickened and edematous. However, although the skin was, occasionally, involved by tumor, it was rarely ulcerated. An important, almost constant, feature was the diffuse nature or multicentricity of the lesion, which usually centered deep in the substance of the breast (Figs. 1 and 2). The axillary nodes were enlarged, and massive malignant involvement was almost uniformly found. The gross appearance of the 10 opposite breasts that had become involved metastatically was not unlike that of the breasts containing the lesions that were primary.

FIG. 1. Inflammatory carcinoma of the breast. Breast is diffusely enlarged and skin over major portion is dark from injection of superficial blood vessels. Edema of subcutaneous tissues is evidenced by deep pitting at sites of hair follicles and sebaceous glands.

For the purpose of determining, mainly, the extent of lymphatic involvement, tissue blocks had been selected from the 50 breasts containing primary lesions and from 10 breasts containing metastatic lesions. In this respect, our search was not designed to be as

FIG. 2. Bisected gross specimen of typical inflammatory carcinoma of the breast showing diffuseness of malignant process.

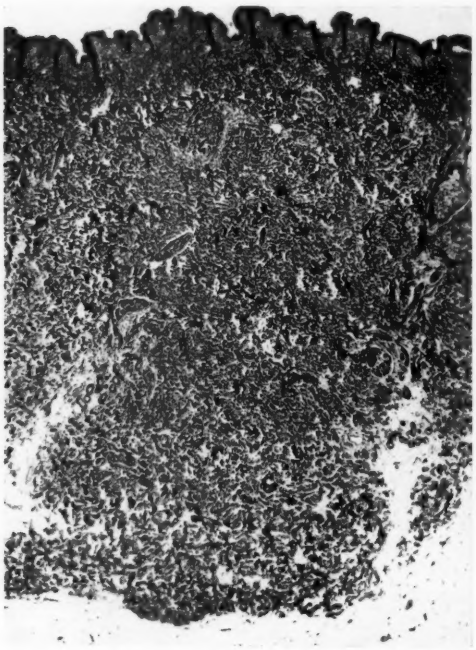


FIG. 3. Thickened and edematous dermis in inflammatory carcinoma of the breast. Hematoxylin and eosin, ×20.

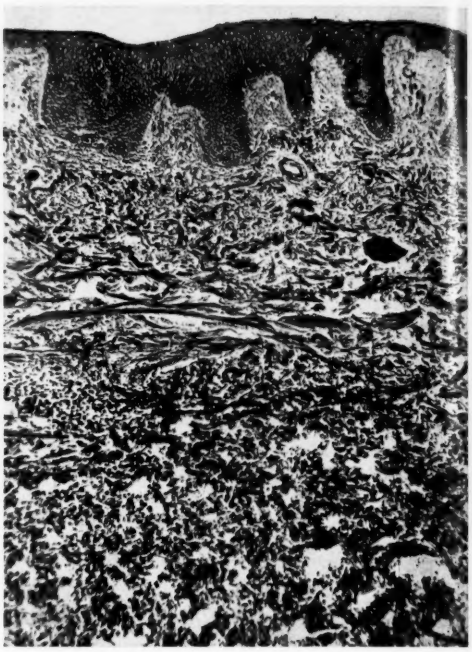


FIG. 4. Clumps of carcinoma cell nests are seen permeating subepithelial lymphatics. Note also surrounding edema of tissue. Hematoxylin and eosin, ×100.

thorough as that carried out by Meyer and his associates. Yet, in 38 of the 50 specimens of primary carcinoma (76 per cent) and in 8 of the 10 specimens of metastatic carcinoma (80 per cent), carcinoma cells were encountered in the subepidermal lymphatic channels (Figs. 3 and 4). This blockage varied from that of massive plugging to that caused by nests containing only a few tumor cells. Seven specimens of primary carcinoma, 14 per cent, in which skin findings were "negative" exhibited deeper lymphatic involvement (Fig. 5). Only 5 primary and 2 metastatic lesions from the 50 patients with large surgical specimens lacked superficial or deep evidence of lymphatic involvement. One of the 3 biopsies of the breast also revealed positive subepidermal findings. Therefore, in 86 per cent of the cases in which the primary or the metastatic lesion had been removed surgically, or in which biopsy had been performed, carcinoma cells were found in the lymphatic channels. We suspect that if more sections had been taken this incidence would have approached 100 per cent.

The edema of the skin, which was so grossly evident, was mainly localized to the dermis. Lymphocytes and plasma cells were present, but not in sufficient numbers to account for the clinical signs on the basis of an inflammatory process. Polymorphonuclear leukocytes were rarely observed.

Forty-five patients had grade 4 adenocarcinomas (Broders' classification). The remaining 8 patients had grade 3 adenocarcinomas, 2 being comedo in type. The grades of the metastatic lesions corresponded to those of the primary lesions. Axillary lymph nodes were metastatically involved in all of 60 axillary dissections available.

Outcome of disease. In addition to axillary metastasis in all 53 patients, 38 ultimately had recurrent or metastatic lesions, or both, at other sites. The commonest site for these

was the skin of the anterior thoracic wall (15). The next most common sites were, in order, the opposite breast (14), the osseous system (13), and the pulmonary system (8). A new, noninflammatory, primary lesion developed in the opposite breast of 1 patient.

Five of 50 patients eligible for 5 year follow-up examination have survived 5 years or more. Two of these died of the disease after surviving approximately 7 years, while 3 are alive without recurrent disease after 5.6, 8, and 10 years, respectively.

The 14 patients who had bilateral inflammatory disease on admission, or had it later, survived an average of 20.3 months after treatment. Ten of these patients were treated surgically. The 4 patients who exhibited bilateral malignancy on admission survived an average of 16.5 months after therapy; 3 of these were treated surgically.

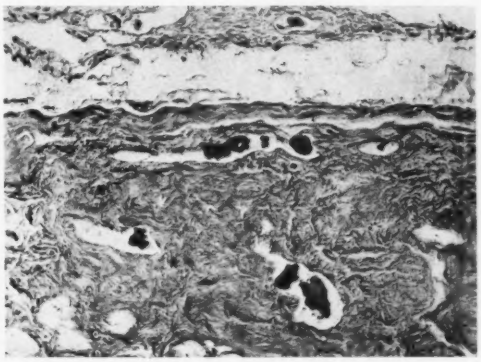


FIG. 5. Retrograde permeation of lymphatic channels in ligaments of Cooper. Hematoxylin and eosin, ×75.

COMMENT

The age distribution of patients with inflammatory carcinoma of the breast seems to be similar to that of carcinoma of the breast in general. Although all patients in the present series were females, Meyer and his associates have reported the disease as occurring in males.

We concur in the observation that pregnancy and lactation do not particularly predispose to the development of this disease. Ten of the 53 patients in our series were nulliparous, and only 1 of the parous patients had noticed the onset of symptoms during pregnancy and lactation.

In this series, 7.5 per cent of the patients had bilateral, simultaneous disease, and an additional 18.9 per cent eventually had typical clinical and pathologic findings indicating spread to the opposite breast. Harrington reported an incidence of 6 to 8 per cent for bilaterality in carcinoma of the breast. Rogers and Fitts found that the disease developed bilaterally in 30 per cent of their patients with inflammatory carcinoma of the breast.

Clinical observers seem to disagree as to the basis for a diagnosis of inflammatory carcinoma of the breast. We believe, as does Haagensen, that one criterion to be insisted on is the presence of both edema and redness that involve at least a third of the mammary area, and we observed this criterion in the selection of cases in our series. One should exclude those cases in which edema and redness are associated with bulky lesions that directly involve the skin or cause it to ulcerate and become secondarily infected.

Various authors have demonstrated that inflammatory carcinoma invades blood vessels as well as lymphatic channels, but it is the peculiar predilection for the latter avenue of dissemination, especially permeation of the subepidermal channels, that gives the disease some of its unique clinical features. Carcinoma that blocks the lymphatic channels of the skin prevents drainage of lymph and leads to edema of the skin. This blockage can cause increased tissue tension with resultant passive hyperemia to account for the constant feature of redness. Involvement deep into the lymphatic channels contributes substantially to the enlargement of the entire breast that is seen so frequently in inflammatory carcinoma. The question why carcinomas of the breast with associated edema do not all concomitantly exhibit redness may be answered by saying only that inflammatory carcinoma has a higher malignant or invasive potential than does ordinary carcinoma.

Reported results of treatment for inflammatory carcinoma of the breast have been far from satisfactory; few 5 year survivals have been documented. The fact that in the present series 5 of 50 patients have survived 5 years or more would suggest that a more positive surgical attack on this highly malignant form of carcinoma is indicated. We believe that carcinoma present simultaneously in both breasts can be treated surgically provided there is no medical contraindication.

SUMMARY

In a series of 53 cases of inflammatory carcinoma of the breast encountered at the Clinic during the 11 year period, 1946 through 1956, the peak incidence was in the sixth decade of life and the commonest symptoms were breast pain, mass, swelling, and redness. Both redness and edema each involved an area greater than one-third of the breast. The average preoperative duration of symptoms was 2.9 months. Fourteen patients had bilateral, metastatic inflammatory carcinoma either on admission or subsequently. Thirteen of the patients had been initially treated as having benign disease of the breast, which contributed to unnecessary, avoidable delay of therapy. Metastasis was common; all patients had involvement of the axillary lymph nodes, and 38 eventually had metastatic lesions in other parts of the body as well. Pathologically, the lesions were mostly diffuse high grade adenocarcinomas which in 86 per cent of cases involved and blocked the lymphatic channels of the breast, therefore, probably accounting for the clinical features of edema and redness.

This type of carcinoma behaves in a highly lethal manner, with the majority of patients dying of their disease in an average time of 25 months after treatment. Present day treatment is far from satisfactory. We believe that the only hope for improving the too frequently discouraging results is bolder surgical treatment of the disease when it is first seen.

REFERENCES

1. Chris, S. M. Inflammatory carcinoma of the breast; review of 20 cases and review of literature. Brit. J. Surg., 1950, 38: 163–174.
2. Fitts, W. T., Jr. Inflammatory carcinoma of the breast. Surg. Gyn. Obst., 1958, 107: 95–96.
3. Haagensen, C. D. Diseases of the Breast. Philadelphia and London: W. B. Saunders Co., 1956.
4. Harrington, S. W. Survival rates of radical mastectomy for unilateral and bilateral carcinoma of the breast. Surgery, 1946, 19: 154–166.
5. Lee, B. J., and Tannenbaum, N. E. Inflammatory carcinoma of the breast; a report of twenty-eight cases from the breast clinic of the Memorial Hospital. Surg. Gyn. Obst., 1924, 39: 580–595.
6. Meyer, A. C., Dockerty, M. B., and Harrington, S. W. Inflammatory carcinoma of the breast. Surg. Gyn. Obst., 1948, 87: 417–424.
7. Rogers, C. S., and Fitts, W. T., Jr. Inflammatory carcinoma of the breast; a critique of therapy. Surgery, 1956, 39: 367–370.
8. Taylor, G. W., and Meltzer, A. Inflammatory carcinoma of the breast. Am. J. Cancer, 1938, 33: 33–49.
9. Treves, Norman. The inoperability of inflammatory carcinoma of the breast. Surg. Gyn. Obst., 1959, 109: 240–242.

A CLINICAL AND HISTOPATHOLOGIC STUDY OF ORAL LEUKOPLAKIA

WILLIAM G. SHAFER, D.D.S., Indianapolis, Indiana, and
CHARLES A. WALDRON, D.D.S., Atlanta, Georgia

LEUKOPLAKIA is a term that has been used for many years to indicate a condition of mucous membranes characterized by the appearance of abnormal white patches or plaques. However, there is a universal lack of agreement among clinicians and even pathologists as to the exact meaning of the term. In some instances, leukoplakia is used only to describe a white patch on the mucosa which will not rub off. At the opposite extreme, the diagnosis of leukoplakia may be based upon strict histologic criteria and such a diagnosis often will be made even though clinically the lesion does not appear as a white patch.

There is an increasing belief that the use of the term even should be discontinued or at least redefined because of this lack of unanimity, especially since the word leukoplakia has come to imply and even be synonymous with premalignancy in the minds of many.

There is general agreement that a certain, although disputed, percentage of cases of leukoplakia do undergo transformation into epidermoid carcinoma. For this reason, means of distinguishing clinically between the innocuous white patch and the potentially malignant one have always been of great interest and importance.

The bulk of the statistical information concerning the malignant potential of leukoplakia, however, has been secured from cancer patients who have coexisting leukoplakia. There is little information based on factual studies regarding the percentage of patients with clinical leukoplakia that may be expected ultimately to develop carcinoma in such an area. While estimates in the literature vary from 2.5 to 100 per cent, review of the publications of 28 authors from the older literature indicate a reported average incidence of 30 per cent malignant transformation in cases of leukoplakia according to MacKee and Cipollaro. More recent publications by Cooke and Renstrup, as well as our own personal experience, cast considerable doubt on an incidence of such magnitude. Robinson (19, 20) also believes that only a small percentage of cases of clinical leukoplakia develop into carcinoma and questioned whether the association of cancer and leukoplakia is really proved, suggesting that the profession has been overzealous in diagnosis and use of the term "precancerous." In contrast, Weisberger recently has reported a 4 year study of 22 patients with microscopically confirmed leukoplakia and found that carcinoma developed in 36 per cent of these in the leukoplakic area. Unfortunately, the criteria used for the diagnosis of leukoplakia were not clearly stated.

More reliable data are available on the incidence of persons with oral carcinoma who have coexistent leukoplakia. Weisberger has reported that 60 per cent of 275 patients with oral carcinoma presented leukoplakia adjacent to the cancer. Trieger and associates reported that of 108 patients with carcinoma of the tongue, only 16 (14.8 per cent) had leukoplakia as well. Reports by Eichenlaub, Martin and Sugarbaker, Sharp and Spickerman (23), Ackerman (1), Gibbel and associates, Wilkins and Vogler, Moertel and Foss, and Smith indicate a range of from 2 to 75 per cent of patients with oral carcinoma having coexisting leukoplakia.

These reports emphasize the current con-

TABLE I.—OCCURRENCE OF ORAL LEUKOPLAKIA BY AGE AND SEX*

	Male†		Female‡		Total	
Decade	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
1st	0	0	0	0	0	0
2nd	3	1.4	3	2.9	6	1.9
3rd	11	5.0	3	2.9	14	4.4
4th	24	11.0	16	15.7	40	12.5
5th	46	21.0	26	25.5	72	22.4
6th	53	24.4	28	27.4	81	25.2
7th	64	29.2	18	17.6	82	25.5
8th	15	6.9	7	6.9	22	6.9
9th	3	1.4	1	1.0	4	1.2
Total: No.	219		102		321	
Per cent.	68.2		31.8		100	

*Age or sex not specified in some cases.
†Per cent of lesions in males only.
‡Per cent of lesions in females only.

sensus of many workers that it is impossible to determine the incidence of cases of leukoplakia which will undergo malignant transformation just as it is impossible for the clinician to determine with any certainty which cases of leukoplakia are potentially dangerous. It should be emphasized also that the reports available in the literature generally refer to selected groups of individuals, i.e., most of whom already have carcinoma. There is no valid information available concerning the incidence of leukoplakia in a large population group.

A more recent review of the literature by Waldron and Shafer revealed a paucity of information regarding the clinical-pathologic correlation of oral leukoplakia. In an attempt to clarify some of these problems, a review of the clinical-pathologic features of oral leukoplakia as encountered in the tissue diagnostic services of two dental schools has been undertaken. It should be emphasized that this material was derived from a large group of ambulatory, presumably well individuals who presented themselves for dental care at the clinics of the dental schools or at the offices of private practitioners of dentistry. The lesions in question often were detected during the course of routine oral examinations and were seldom the chief complaint.

Inasmuch as the criteria for the diagnosis of leukoplakia generally have not been clearly specified in the literature, the term leukoplakia as used in this study will imply only a white patch on the mucosa and will carry no histologic connotation. Care was taken in excluding from the designation of leukoplakia such well recognized oral manifestations or entities as lichen planus, syphilitic mucous patches, white sponge nevus or white folded gingivostomatitis, mycotic infections, chemical burns, lupus erythematosus, psoriasis, and many other stomatitides.

MATERIALS AND METHOD

The materials utilized in this study consisted of biopsy and surgical specimens from the tissue diagnostic services of the Departments of Oral Pathology, Indiana University School of Dentistry and Emory University School of Dentistry. The periods covered were 1 October 1950 through 31 March 1960 (Indiana) and 7 July 1950 through 31 March 1960 (Emory). The total number of specimens processed in these two laboratories during the respective periods was 8,554.

Oral lesions suitable for inclusion in this study were derived from those cases which had been coded either as leukoplakia, hyperkeratosis, parakeratosis, acanthosis, leukedema, spongiosis, or any combination of these. Case histories submitted with the tissue were examined, and only those specimens were selected for use in which the dentist had indicated that the lesion clinically was leukoplakia, keratosis, or a white patch and which was thought clinically not to represent a malignant lesion. However, in some cases in the latter group as well as in others, the dentist had performed a biopsy of the lesion for the purpose of ruling out cancer.

Three hundred thirty two biopsy specimens from 286 separate patients were suitable for inclusion in this study. In occasional cases, biopsies of specimens from 2 or more areas in the oral cavity had been performed at the same time. These were treated as separate specimens. In addition, a very few patients had had biopsies over a rather prolonged period of time. In 1 instance, a man had had 17 biopsies of specimens from different sites in the oral cavity over 9 years.

All cases coded as "lichen planus" or "compatible with lichen planus" were also examined because of their clinical similarity to leukoplakia. Of 38 cases, it was found that 12 had been correctly diagnosed clinically as lichen planus, 9 had been diagnosed clinically as leukoplakia or a keratotic lesion, while 17 had been described only as white lesions, with no attempt at clinical diagnosis. None of these 38 cases was included in the present study, however.

All tissue specimens utilized in this study were reviewed by both authors and agreement reached in each case. No difficulty was encountered in establishing criteria for the microscopic diagnosis except in the case of focal atypia, dyskeratosis, and carcinoma in situ, and this will warrant further discussion.

RESULTS

The 332 tissue specimens of oral white lesions included in this study represent approximately 4 per cent of the total number of specimens processed in these two laboratories during the intervals stated. Considering the large number of specimens processed which represented purely dental infections (e.g., periapical granulomas and cysts), this percentage is relatively high and indicative of the clinical extent and significance of this lesion.

Age and sex. Most reports, for example, those of Sturgis and Lund, Hobaek, and Renstrup, state that leukoplakia is more common in men than in women, and that it is a disease chiefly of older individuals. Renstrup found that 90 per cent of 90 patients in one study were past 40 years of age, while Hobaek reported an average of 60.1 years for his 246 cases. Weisberger also has stated that the highest incidence of leukoplakia occurs in the fourth to sixth decades of life.

In the present study, the occurrence of clinical leukoplakia in females was found to be considerably higher than has been generally believed, nearly 32 per cent (Table I). While occasional cases occurred in the second decade, the vast majority were seen in the fifth to seventh decades. Approximately 81 per cent of the patients in this study were over 40 years of age. It was interesting that there appeared to be a slight trend for earlier occurrence of leukoplakia in females. Too few patients other than Caucasians were represented in this study to be able to draw any conclusions regarding racial occurrence.

TABLE II.—SITES OF ORAL LEUKOPLAKIA

	Male*		Female†		Total	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Upper lip	0	0	0	0	0	0
Lower lip	25	11.0	1	1.0	26	7.8
Max. ridge, gingiva, and mucobuccal fold	19	8.3	12	11.5	31	9.3
Mandibular ridge, gingiva and mucobuccal fold	56	24.6	39	37.5	95	28.6
Buccal mucosa	45	19.7	20	19.2	65	19.6
Palate	21	9.2	14	13.5	34	10.5
Tongue	14	6.1	2	1.9	16	4.8
Floor of mouth	19	8.3	8	7.7	27	8.1
Retromolar	16	7.0	5	4.8	21	6.3
Unspecified	13	5.7	3	2.9	16	4.8
Total: No.	228		104		332‡	
Per cent.	68.7		31.3		100	

*Per cent of lesions in males only.
†Per cent of lesions in females only.
‡Multiple locations in the same patient with biopsies at same time in a few instances.

Location. Leukoplakia may occur at any site in the oral cavity, although certain areas of predilection have been reported. Multiple areas of involvement are also common, and the extent of the involvement varies from small, well localized, irregular patches to diffuse lesions covering a considerable portion of the oral mucosa. Renstrup stated that the buccal mucosa and commissures were the sites most frequently involved, followed by the alveolar mucosa, tongue, lip, hard and soft palate, floor of the mouth, and gingiva. Hobaek found that the tongue and floor of the mouth were the most frequent sites of occurrence followed by the lower lip, buccal mucosa, palate, and gingiva.

The location of the lesions in this study was of considerable interest (Table II). The greatest number of cases in both men and women occurred on the mandibular alveolar ridge, gingiva, or mucobuccal fold. How-

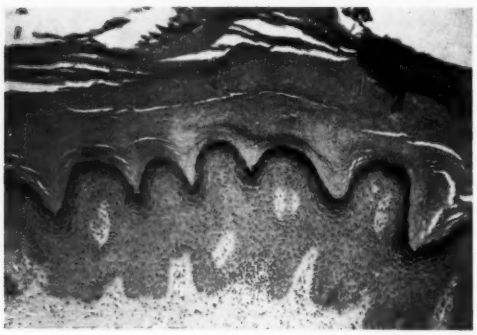


FIG. 1. Hyperkeratosis with thickened prominent granular layer but no remarkable acanthosis.

ever, there was a greater frequency of occurrence in this location among females than among males. This finding is accounted for in a small part at least by the use of snuff among women and its habitual placement in the mandibular mucobuccal fold. Of considerable interest also was the relatively low frequency of occurrence of lesions on the lower lip in females (1.0 per cent) as contrasted to males (11.0 per cent). The tongue generally has been believed to be a common site of occurrence of leukoplakia. However, in both males and females, this was the least frequent site of occurrence in the present series. It is also of interest that no lesions on the upper lip in either sex were found in this study.

Histologic diagnosis. The problem of histologic diagnosis and clinical correlation of leukoplakia has been discussed in a number of recent papers. For example, Renstrup reviewed the biopsy material on 80 patients with clinical leukoplakia and concluded that it was not possible to correlate the histologic changes with the clinical aspects of the condition. Cooke reported that he found little correlation between the various clinical findings as they may present themselves and the histopathology in his cases. Shira emphasized the fact that although some keratotic lesions in the mouth (leukoplakia) are certainly dangerous, most are innocuous and represent only a benign thickening of the oral mucosa developing as a protective mechanism against local stimulation or irritation. He also believed that it was impossible for the clinician to distinguish between the potentially dangerous and the innocuous lesion and emphasized the importance of biopsy in this regard. Kollar and associates emphasized this same point and reported 5 cases to illustrate the danger of inadequate patient management on the basis of leukoplakia as a diagnosis. Although Ward and Sharp (22) have stated that the verrucous, fissured and markedly thickened leukoplakic plaques are the ones most likely to become malignant, Slaughter and associates and Ackerman and Johnson (2) have demonstrated adequately that small, innocuous appearing granular red, gray, or pinkish-gray areas with indefinite margins and without induration often represent carcinoma in situ. Such lesions have been referred to as erythroplasia by Hertz.

The scientific literature includes a wide range of histologic terminology to designate clinical leukoplakia. These terms include keratosis, leukokeratosis, hyperkeratosis, hyperkeratosis simplex, hyperkeratosis complex, nonspecific keratosis, focal keratosis, pachyderma oralis, leukoplakia and intraepithelial carcinoma. Allen, Ash and Raum, Bernier, Hertz, Gorlin, Kerr, and Tiecke require the presence of dyskeratosis before making a microscopic diagnosis of leukoplakia. They imply that a microscopic diagnosis of leukoplakia based upon this criterion carries the possibility or even probability of malignant transformation. In the absence of dyskeratosis, these authors use terms such as focal keratosis and hyperkeratosis for clinical leukoplakia. Cooke, Hobaek, Stones, and Ward have no strict requirement of dyskeratosis for the microscopic diagnosis of leukoplakia.

Hansen points out that the term leukoplakia has a somewhat different meaning for everyone, and this has led to frequent misunderstanding and confusion among clinicians and pathologists. Kollar and associates believe that it would be best to discontinue use of the term leukoplakia as a

microscopic diagnosis because of the serious errors in patient management which can and do occur through misunderstanding of the term.

Histologic criteria. Hyperkeratosis.—There is a moderate amount of keratin present on the surface of normal oral epithelium and this will vary slightly in amount from area to area in the oral cavity depending upon frictional irritation such as toothbrushing and mastication. Hyperkeratosis refers to an abnormal increase in thickness of this keratin layer or stratum corneum in a particular location (Fig. 1). While a keratin layer of a certain thickness may be normal for that area, a layer of the same thickness may be decidedly abnormal for another area.

Parakeratosis.—Parakeratin differs from keratin in the persistence of nuclei or nuclear remnants in the keratin layer. This is also a normal finding in certain areas of the oral cavity. The presence of parakeratin in areas where it is not usually found, or more particularly, a thickening of the parakeratin layer is referred to as parakeratosis (Fig. 2). It is not unusual in the oral cavity to observe alternating areas of keratin and parakeratin or hyperkeratosis and parakeratosis in the same histologic section. The significance of this finding is not known.

Considerable importance is often attached to differentiation between hyperkeratosis and parakeratosis in dermatologic pathology with respect to diagnostic significance. In oral lesions, however, the significance of such differentiation, if any, is still obscure. It has been noted that the presence of a granular layer or stratum granulosum is obvious only in keratinized oral epithelium. When parakeratin is present, the granular layer is almost invariably indistinct or entirely absent. The same is true in hyperkeratosis and parakeratosis. The granular layer is often markedly thickened and extremely prominent in cases of hyperkeratosis but is seldom seen even in cases of severe parakeratosis.

Acanthosis.—The thickness of the spinous layer (the stratum spinosum or prickle cell layer) also varies considerably between different areas of the oral cavity. Thus, a certain thickness may be normal for one area but abnormal for another. Acanthosis refers to the abnormal thickening of the spinous layer for that particular location (Fig. 3). This may be quite severe with elongation, thickening, blunting, and confluence of the rete pegs or may consist only of their elongation. Acanthosis may or may not be associated with hyperkeratosis or parakeratosis, sometimes occurring independent of changes in the overlying layer.

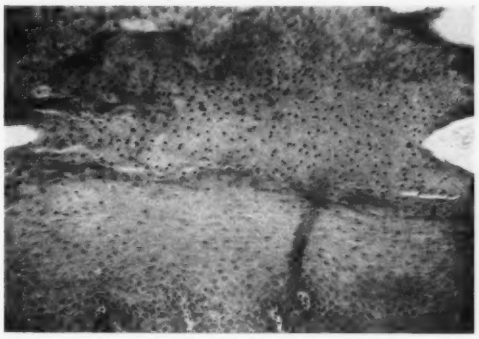


FIG. 2. Parakeratosis with absence of granular layer and very mild acanthosis.

Dyskeratosis.—Numerous criteria exist for the diagnosis of dyskeratosis and there is not always a clear-cut distinction between what represents dyskeratosis in the form of focal atypia and dyskeratosis representing carcinoma in situ (Figs. 4 and 5). Neither do we have knowledge that dysker-

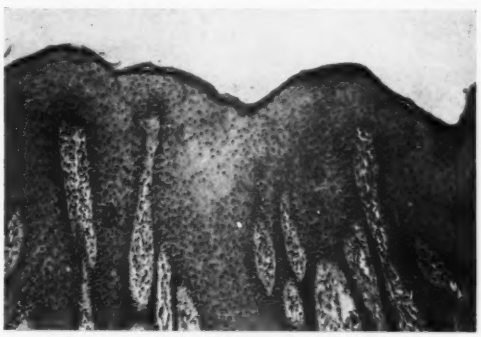


FIG. 3. Acanthosis with no significant hyperkeratosis or parakeratosis.

FIG. 4. Focal atypia or mild dyskeratosis.

atosis represented by focal atypia will inevitably, or even usually, progress to obvious carcinoma in situ. Criteria which have often been used for the diagnosis of dyskeratosis include: (a) increased, and particularly abnormal, mitoses; (b) individual cell keratinization; (c) epithelial pearls within the spinous layer; (d) alterations in the nuclear-cytoplasmic ratio; (e) loss of polarity and disorientation of cells; (f) hyperchromatism of cells; (g) large, prominent nucleoli; (h) dyskaryosis or nuclear atypism including giant nuclei; (i) poikilocarynosis or division of nuclei without division of cytoplasm; and (j) basilar hyperplasia. Distinction must be made between malignant dyskeratosis, characterized by these features, and so-called benign dyskeratosis such as is seen in Darier's disease and molluscum contagiosum.

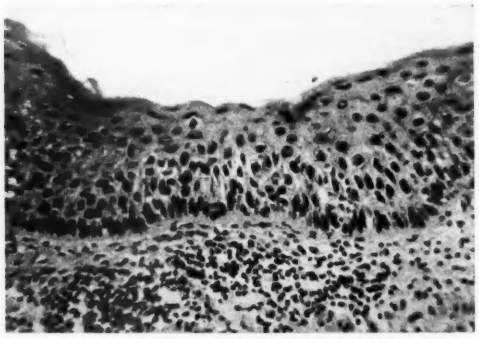


FIG. 5. Focal atypia consisting chiefly of mild basilar hyperplasia, hyperchromatism of nuclei and loss of polarity. There is no hyperkeratosis, or acanthosis.

Carcinoma in situ or intraepithelial carcinoma.—A definitive distinction cannot always be drawn between dyskeratosis and carcinoma in situ. Certain of the criteria listed for dyskeratosis, when encompassing an even greater area than what could be considered focal, when extremely severe in degree, or when exhibiting "top to bottom" change particularly with respect to basilar hyperplasia (Figs. 6 and 7), must undoubtedly be diagnosed as carcinoma in situ, provided of course that there is no true invasion of the connective tissue (Fig. 8).

It is of considerable interest that some intraoral lesions exhibit "top to bottom" basilar hyperplasia, loss of polarity, increased mitoses, hyperchromatism, dyskaryosis, and alterations in nuclear-cytoplasmic ratio without any evidence of thickening of the epithelial layer, or, more significantly, without any evidence of a disturbance of the keratinization process. Thus, in approximately one-half of all lesions coded in our files as carcinoma in situ, there was no individual cell keratinization, no epithelial pearl formation, and no hyperkeratosis. Inevitably these lesions were described clinically as being flat, red, velvety, and having a granular appearance. Our experience has been that intraoral carcinoma in situ is infrequently present as a clinically hyperkeratotic lesion. In some specimens, however, areas of flat, thin, red, carcinoma in situ alternated with areas showing hyperkeratosis or parakeratosis, with or without acanthosis and focal atypia.

Leukedema.—This is an unusual condition characterized by the occurrence of intracellular edema of the spinous cells usually associated with acanthosis (Fig. 9). The term was first applied by Sandstead and Lowe to an abnormality of the buccal mucosa which clinically resembled early leukoplakia. In their original study it was found to be more common in the Negro race, affected both men and women, and could not be related to the use of tobacco, salivary *p*H, infection, or galvanic irritation. The microscopic features were described as acantho-

sis, intracellular edema of the spinous cells, an irregular, amorphous surface without keratinization and broad irregularly elongated rete pegs. The edematous cells were large and pale, while the cytoplasm appeared lost and the nuclei either absent, clear, or pyknotic. A similar, if not identical, histologic picture is found in an unusual disease, sometimes familial, known as white, folded gingivostomatitis or oral white sponge nevus. The significance of leukedema is entirely unknown as is its relationship, if any, to leukoplakia.

Stomatitis nicotina.—This is a condition recognizable both clinically and microscopically. It is characterized by a diffuse grayish-white coloration of the hard palate with multiple papular areas, usually less than 5 millimeters in diameter, each with a central depressed red spot. These red spots represent dilated and sometimes partially occluded orifices of the minor salivary gland ducts of the palate around which inflammatory cell infiltration is quite prominent (Fig. 10). This is considered by many investigators as simply an anatomic variant of leukoplakia.

Histologic findings. There are remarkably few significant studies other than isolated case reports demonstrating a clinicopathologic correlation of leukoplakia. Most authors have described in detail either the clinical features of the disease or the histologic picture of various white lesions. Few have presented the microscopic findings of oral lesions diagnosed clinically as leukoplakia from a sizable group of patients. For this reason, there is little significant information available to indicate the incidence of serious histologic changes in any given series of patients with clinical leukoplakia. Renstrup has reported one of the largest such series in which biopsies were taken from 80 patients with lesions diagnosed clinically as leukoplakia. The specimens showed hyperkeratosis and parakeratosis in 89 per cent of the patients; acanthosis was next in frequency in 30 per cent, and dyskaryosis was present in 2.5 per cent of patients. Inflammatory cell infiltration of the underlying connective

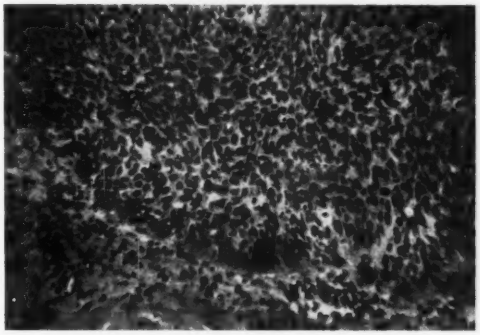


FIG. 6. Dyskeratosis consisting chiefly of severe basilar hyperplasia: carcinoma in situ.

tissue was present in 54 per cent of the biopsies. The presence of inflammation in leukoplakia has been noted and discussed by many; however, the significance of this finding is not understood and possibly may not be related to the lesion per se.

The vast majority of cases in this current study (approximately 85 per cent of the 332 specimens) consisted of perfectly benign and innocuous lesions characterized by hyperkeratosis and acanthosis, parakeratosis and acanthosis or hyperkeratosis alone (Table III). (Percentages could not be calculated throughout because there was overlap in some cases, e.g., certain lesions presented areas of both hyperkeratosis and parakeratosis.) A few lesions showed only acanthosis or only parakeratosis. It was of in-

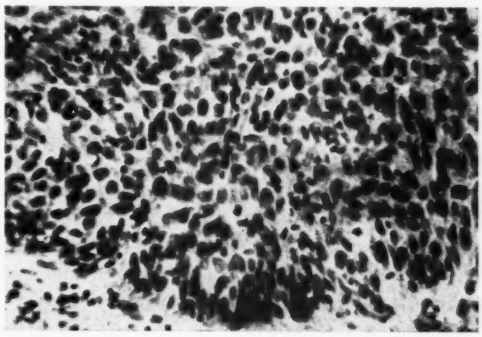


FIG. 7. Dyskeratosis with severe basilar hyperplasia also exhibiting hyperchromatic nuclei, cellular pleomorphism, loss of polarity and increased mitoses: carcinoma in situ.

FIG. 8. Severe dyskeratosis representing all changes of carcinoma in situ with early invasion of connective tissue.

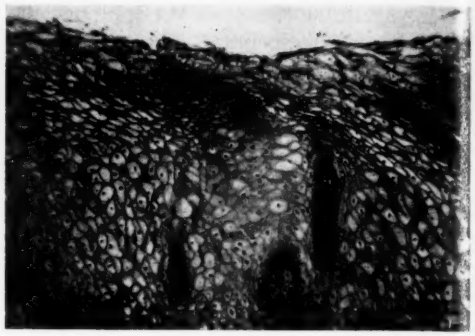


FIG. 9. Leukedema with typical vacuolated cells and pyknosis of nuclei associated with acanthosis can be seen in this photomicrograph.

terest that parakeratosis alone was relatively uncommon in contrast to hyperkeratosis alone, whereas parakeratosis in association with acanthosis was seen more frequently than hyperkeratosis with acanthosis.

There appeared to be no real differences in the occurrence of the different forms of epithelial dysplasia between men and women except for the greater preponderance of carcinoma in men, a well recognized clinical phenomenon. The condition known as leukedema did occur far more frequently in men, confirming the observation of Sandstead and Lowe. Inflammation was present in nearly all specimens in this series and for this reason was disregarded.

In only 26 cases (approximately 7.8 per cent) was focal atypia associated with any of these conditions. Six cases of carcinoma in situ (extreme dyskeratosis) and 27 cases of invasive carcinoma, all clinically diagnosed as leukoplakia, were found in this series. Together these represented 17.7 per cent of all white lesions biopsied (excluding lichen planus and all other specific entities).

Data regarding the relation between leukoplakia and possible etiologic agents were insufficient to draw conclusions, generally since such information was not included routinely in the histories accompanying the tissue specimens. However, a note was made that 36 of the patients in the series (29 men and 7 women) were heavy smokers, 9 patients (all men) were tobacco chewers and 14 patients (4 men and 10 women) used snuff. Tooth or denture irritation was specifically noted in 9 cases (5 men and 4 women), Plummer-Vinson syndrome was present in 1 woman, and 1 man had a past history of syphilis. In addition, at least 3 patients (2 men and 1 woman) had a history of previous oral cancer.

TABLE III.—HISTOLOGIC INTERPRETATION OF WHITE LESIONS

	Male	*Female*	*Total**	
	No.	*No.*	*No.*	*Per cent*
Hyperkeratosis without acanthosis	57	30	87	26.2
Parakeratosis without acanthosis	10	8	18	5.4
Acanthosis only	5	1	6	1.8
Hyperkeratosis with acanthosis	59	26	85	25.6
Parakeratosis with acanthosis	71	34	105	31.6
Hyperkeratosis, parakeratosis, acanthosis with focal atypia	18	8	26	7.8
Carcinoma in situ (extreme dyskeratosis)	5	1	6	1.8
Carcinoma, invasive	21	6	27	8.1
Leukedema with or without hyperkeratosis, parakeratosis, or acanthosis	26	4	30	9.0

*The percentage totals more than 100 since some of the 332 lesions exhibited both hyperkeratosis and parakeratosis, with or without acanthosis, and were tabulated separately.

DISCUSSION AND CONCLUSIONS

There is considerable justification for the proposal of certain authors to restrict use of the term leukoplakia to only the clinical description of a lesion if one would consider the derivation of the word itself, "a white plate." Thus, in this strict sense of the word,

there would be no histologic connotation. Furthermore, much of the existing confusion in terminology, in diagnosis, and in treatment would be abolished if only microscopic terms were to be used in the microscopic diagnosis of oral white lesions. For example, the diagnosis of hyperkeratosis and dyskeratosis would immediately identify to the clinician the nature of the epithelial dysplasia with which he is dealing and imply a condition of at least potentially greater immediate seriousness than a diagnosis of hyperkeratosis and acanthosis. This would eliminate any misunderstanding as to the variation in meaning of the term leukoplakia between different pathologists since most pathologists agree on the definition of the microscopic terms.

There also seems to be considerable justification for the doubt existing in the minds of many that the term leukoplakia should imply a premalignant condition. While a certain small percentage of these white lesions do show atypical cellular alterations suggesting that they ultimately may undergo malignant transformation, the vast majority present no remarkable cellular deviations and, in fact, resemble nothing more than a callus on skin surfaces. Inasmuch as no follow-up was possible in the present series of cases, it is impossible to prognosticate the ultimate outcome of even the most benign appearing of the lesions. Still it seems most unlikely that more than a very small percentage will ever present a serious clinical problem. Of greater interest and deeper concern to the clinician should be the more innocent-appearing red granular lesions which experience has shown more frequently to represent either carcinoma in situ or early invasive cancer.

The fact that 8.1 per cent of these keratotic lesions were actually invasive carcinomas, however, is of considerable significance. Although, in some of these cases the clinician noted the possibility that the lesion might represent carcinoma, none of the carcinomas included in this study presumably were clinically obvious.

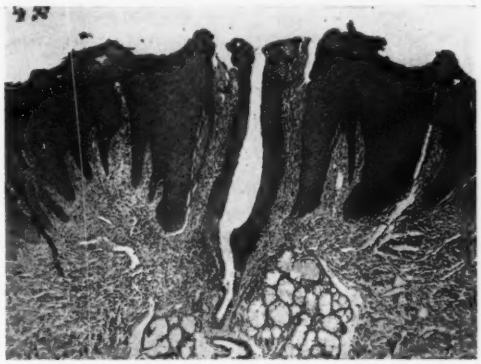


FIG. 10. Stomatitis nicotina. The tissue section is cut fortuitously through a duct associated with the accessory palatal salivary gland tissue. There is hyperkeratosis of adjacent mucosa and inflammation of the subjacent connective tissue.

The fact that experienced clinicians are not able to differentiate the innocuous white patch from the dangerous lesion on clinical grounds demonstrates the importance of adequate biopsy examination in the management of oral leukoplakia. These findings emphasize the danger of the practice of "watchful waiting" or clinical observation of leukoplakia. Too often we all have seen patients with advanced oral carcinoma who report that a dentist or physician has been watching an area of leukoplakia for long periods.

SUMMARY

1. Confusion regarding the clinical and microscopic use of the term leukoplakia has been discussed as well as the implication of the term premalignancy. The literature on oral leukoplakia also has been reviewed, particularly that dealing with clinicopathologic correlations.

2. All cases of leukoplakia or oral white lesions in the Departments of Oral Pathology, Schools of Dentistry at Indiana University and Emory University have been reviewed. Data have been presented regarding age, sex, sites of occurrence, and microscopic findings in 332 specimens from 286 patients.

3. The vast majority of cases of clinical

leukoplakia are perfectly benign histologically and, at the time of examination at least, exhibit no premalignant features.

4. A smaller but significant number of lesions presenting as clinical leukoplakia were found to be invasive carcinoma on histologic examination.

5. We support the proposal made by others that the term leukoplakia be discontinued as a microscopic diagnosis, be replaced by microscopic terms which can be defined and on which there is general agreement, and that the term be reserved for the clinical description of a white lesion on the mucous membrane.

REFERENCES

1. Ackerman, L. V. Verrucous carcinoma of the oral cavity. Surgery, 1948, 23: 670.
2. Ackerman, L. V., and Johnson, R. Present day concepts of intraoral histopathology. Proceedings of the Second National Cancer Conference, American Cancer Society, Inc., 1954.
3. Allen, A. C. The skin; a clinicopathologic treatise. St. Louis: The C. V. Mosby Co., 1954.
4. Ash, J. E., and Raum, M. An atlas of otolaryngic pathology. American Registry of Pathology—Armed Forces Institute of Pathology, Washington, D. C., 1956.
5. Bernier, J. L. Tumors of the lips. Dent. Clin. North Am., 1957, p. 657.
6. Cooke, B. E. D. Leukoplakia buccalis and oral epithelial naevi; a clinical and histological study. Brit. J. Derm. Syph., 1956, 68: 151.
7. Eichenlaub, F. J. Leukoplakia buccalis. Arch. Derm. Syph., Chic., 1938, 37: 590.
8. Gibbel, M. S., Gross, J. H., and Ariel, I. M. Cancer of the tongue; a review of 330 cases. Cancer, 1949, 2: 441.
9. Gorlin, R. J. Tumors of the buccal and labial mucosa. Dent. Clin. North Am., 1957, p. 681.
10. Hansen, L. S. Diagnosis of oral keratotic lesions. J. Oral Surg., 1959, 17: 60.
11. Hertz, J. Oral precancerous lesions. Oral Surg., 1956, 9: 687.
12. Hobaek, A. Leukoplakia oris. Acta odont. scand., 1946–1947, 7: 61.
13. Kerr, D. A. Keratotic lesions of oral cavity. J. Dent. M., N. Y., 1958, 13: 92.
14. Kollar, J. A., Jr., Finley, C. W., Nabers, J. M., Ritsbey, B., and Orban, B. J. Leukoplakia. J. Am. Dent. Ass., 1954, 49: 338.
15. MacKee, G. M., and Cipollaro, A. C. Cutaneous Cancer and Precancer; a Practical Monograph. New York: American Journal of Cancer, 1937.
16. Martin, R. E., and Sugarbaker, E. D. Cancer of the floor of the mouth. Surg. Gyn. Obst., 1940, 61: 347.
17. Moertel, C. G., and Foss, E. L. Multicentric carcinomas of oral cavity. Surg. Gyn. Obst., 1958, 106: 652.
18. Renstrup, C. Leukoplakia of the oral cavity. Acta odont. scand., 1958, 16: 99.
19. Robinson, H. B. G. Practical application of experimental cancer research. J. Am. Dent. Ass., 1957, 54: 524.
20. Idem. Neoplasms; precancerous lesions of the oral regions. Dent. Clin. North Am., 1957, p. 621.
21. Sandstead, H. R., and Lowe, J. W. Leukoedema and keratosis in relation to leukoplakia of buccal mucosa in man. J. Nat. Cancer Inst., 1953, 14: 423.
22. Sharp, G. S. Cancer of the oral cavity. Oral Surg., 1948, 1: 614.
23. Sharp, G. S., and Spickerman, W. D. Cancer of the tongue. Am. J. Roentg., 1947, 57: 161.
24. Shira, R. B. Diagnosis of common lesions of the oral cavity. J. Oral Surg., 1957, 15: 95.
25. Slaughter, D. P., Southwick, H. W., and Smejkal, W. Field cancerization in oral stratified squamous epithelium. Cancer, 1953, 6: 983.
26. Smith, J. F. Carcinoma of the gingivae. J. Tennessee Dent. Ass., 1959, 39: 236.
27. Stones, H. H. Oral and dental diseases. 3rd ed. Edinburgh and London: E. & S. Livingstone Ltd., 1954.
28. Sturgis, S. N., and Lund, C. C. Leukoplakia buccalis and keratosis labialis. N. England J. M., 1934, 210: 996.
29. Tiecke, R. W. Tumors of the tongue and floor of the mouth. Dent. Clin. North Am., 1957, p. 697.
30. Trieger, N., Ship, I. I., Taylor, G. N., and Weisberger, D. Cirrhosis and other predisposing factors in carcinoma of the tongue. Cancer, 1958, 11: 357.
31. Waldron, C. A., and Shafer, W. G. Current concepts of leukoplakia. Internat. Dent. J., 1960, 10: 350.
32. Ward, G. E. Leukoplakia; ca—a bulletin of cancer progress. Am. Cancer Soc., 1953, 3: 131.
33. Weisberger, D. Precancerous lesions. J. Am. Dent. Ass., 1957, 54: 507.
34. Wilkins, S. A., Jr., and Vogler, W. R. Cancer of gingiva. Surg. Gyn. Obst., 1957, 105: 145.

THE VASCULAR RESPONSE TO REPEATED FRACTURE

JAMES B. WRAY, M.D., Syracuse, New York

FRACTURE OF A LONG BONE in the experimental animal sets in motion a series of regional circulatory alterations marked by an immediate increase in blood flow into the limb, gradual enlargement of the vascular bed of the entire limb, and proliferation of vessels at the fracture site leading to vascularization of the fracture callus.

The initial experimental evidence of dramatic changes in the circulatory environment around a fracture site was published by Lexer in 1922. Roentgenograms of a fractured limb of a dog taken after intravascular injection of a radiopaque mixture of turpentine and mercury revealed a marked increase in vascularity around the site of the fracture. Although limited by rather crude techniques, Lexer concluded that the phenomena represented a characteristic response to fracture and, further, was essential to fracture healing.

Work published in 1959 by Wray and Lynch (5) quantitatively established the existence of postfracture hypertrophy of the vascular bed and indicated that the entire limb was involved in the process. A rapid rise in vascular bed volume developed to a peak at about 9 days after fracture and seemed to recede with healing of the fracture.

Because of the demonstration by Wray and Spencer (6) of an immediate vasodilatory response to fracture in the dog, further experimental work was instituted in an effort to clarify those factors leading to regional vascular bed hypertrophy after fracture of a long bone.

The data obtained in experiments upon a large series of rats subjected to repeated refracture of the tibia are presented herein in an effort to shed some light upon the pathogenesis of some of the vascular changes seen after fracture.

From the Bowman Gray School of Medicine, Winston Salem, North Carolina.

This investigation was supported by National Institutes of Health Grant A-2936.

MATERIALS AND METHODS

Three hundred and eighty-two 5 month old male albino rats of the C. F. Nelson strain were used in this experiment. All animals were obtained from the same supplier and were maintained on a standard laboratory diet while housed in steel cages in groups of 10.

In all animals, except the controls, a closed fracture of the left tibia was produced by finger manipulation under ether anesthesia. Those animals in which either a break appeared in the skin or there was no evidence of fracture upon roentgenographic examination after death were excluded from the series.

The experimental animals were divided into 4 major groups labeled A, B, C, and D. In group B, the fracture was remanipulated at 9 days after the original fracture; in group C at 9 and 18 days; and in group D at 9, 18, and 27 days after original fracture. Great care was taken to remanipulate through the primary fracture site and, in each case, remanipulation was carried out until the fracture site was mobile. No effort was made to immobilize the fractures, and the animals were allowed to run free in their cages.

Both the experimental and control animals were sacrificed with an overdose of ether. After death, the sternum was resected and the thoracic aorta cannulated with a polyethylene catheter to permit injection of the lower trunk and hind limbs with methyl methacrylate. The details of this technique have been published elsewhere and will not be repeated herein.

After the plastic hardened, the cadaver was skinned and the hind limbs of the ani-

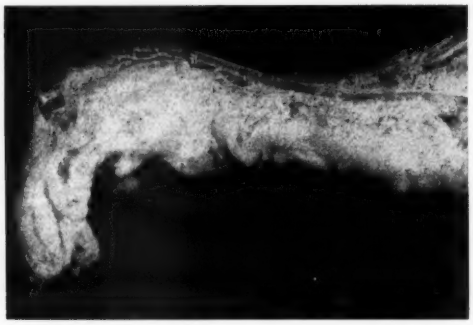


FIG. 1. Magnified 3 times, this photograph shows the plastic mold of the vascular bed of the hind foot of one of the experimental animals. After the injected plastic has hardened, the hind limbs are disarticulated at the hip and then immersed in 5 per cent potassium hydroxide solution for 72 hours. The limb is then treated with 30 per cent hydrochloric acid solution to leave only the plastic mold of the vascular bed. Vessels down to and including capillary size are injected by this technique.

mal were disarticulated at the hip joints with a technique which was constant throughout the experiment. The disarticulated limbs were then macerated in a 5 per cent solution of potassium hydroxide for a period of 72 hours, followed by a 30 per cent solution of hydrochloric acid for 24 hours.

The chemical digestion removed all animal tissues and only the plastic cast of the vascular bed of the entire limb remained (Fig. 1). This cast was allowed to dry and then weighed on an analytic balance scale. The weight of the plastic cast of each limb was compared with the weight of the cast of the opposite paired limb. All data were subjected to statistical analysis.

TABLE I.—DATA OBTAINED FROM THE EVALUATION OF 382 RATS

	Days after last fracture	*No. of animals*	*Mean difference between paired limbs*	*Probability that experimental and control means differ by chance alone*
	Controls	38	.0032	
	6	15	+.0256	< .6 >.5
	9	17	−.1183	<.001
Group A	12	17	−.0755	<.05>.02
82 rats	15	17	−.1307	<.01>.001
	24	16	−.0908	<.001
	6	18	−.1518	<.001
Group B	9	17	−.1055	<.05>.02
89 rats	12	18	−.1179	<.05>.02
	15	18	−.0848	<.02>.01
	24	18	−.0480	< .3>.2
	6	18	−.1501	<.001
Group C	9	17	−.0993	<.2>.1
88 rats	12	17	−.0775	<.01>.001
	15	18	−.0872	<.001
	24	17	−.0637	<.05>.02
	6	17	−.1072	<.01>.001
Group D	9	17	−.0093	<.9>.8
85 rats	12	17	−.2040	<.01>.001
	15	17	−.0331	< .5>.4
	24	17	+.0102	< .8>.7
	Total	382		

Group A rats had 1 fracture of the left tibia while in group B, C, and D, 1, 2, and 3 refractures, respectively, were carried out.

RESULTS

Data obtained from the studies on the 382 rats are presented in Table I. Thirty-eight animals were used as controls, and the remainder were divided into 4 approximately equal groups labeled A, B, C, and D. Each group was subdivided into smaller groups to be sacrificed at 6, 9, 12, 15, and 24 days after the last fracture. As indicated in the discussion of the technique, the animals in group A were fractured once only, while in groups B, C, and D remanipulation was carried out 2, 3, and 4 times, respectively at 9 day intervals.

Data labeled "mean difference between paired limbs" were obtained by averaging the difference between paired limbs in each group when the weight of the plastic cast of the left leg was subtracted from the weight of the plastic cast of the right limb (Table I). A minus value thus indicates that the plastic cast of the left fractured limb was heavier than that of the right unfractured side.

The values are listed when the differences in weight of the paired control limbs are compared with the differences noted in individual groups of rats. The probability that the control differences and the experimental differences differ by chance alone is also given in the tabulation.

When .05 was considered as the accepted level of significance, a significant increase in vascular bed volume on the fractured side did not occur until day 9 in group A. On the other hand, in groups B, C, and D significance was reached by the sixth day which indicates an overlapping response to the basic enlargement stimulus.

In all groups significant vascular bed enlargement was noted 12 days after fracture.

A graphic representation of the data is given in Figure 2 in which the value of the mean differences between paired limbs is plotted in milligrams against the time in days after fracture. The time intervals listed in each group represent the time that elapsed since the last fracture in that group.

Several points should be noted after the first refracture; the vascular volume of group B climbed to even higher levels than that at the same time after fracture in group A. An essentially similar response was noted in group C and a very high peak volume in group D. The vascular volume high, in all groups, followed the last fracture manipulation by 9 to 12 days.

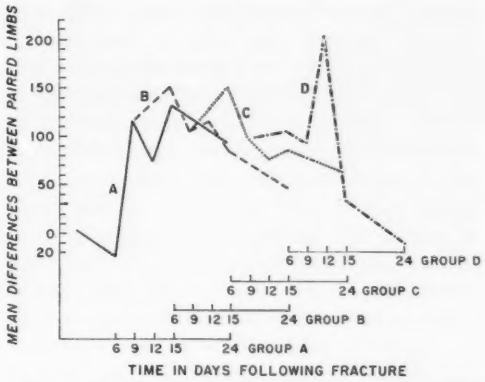


FIG. 2. Graph showing the mean differences between paired fractured and unfractured limbs plotted against the time elapsed since the last fracture in each group. Whereas the left tibia of rats in group A was fractured only once; in groups B, C, and D, 1, 2 and 3 refractures, respectively, were carried out.

DISCUSSION

Vascular beds have been shown to exhibit two types of distensibility. The first is characterized by a rapid adjustment to briefly maintained increases in pressure or blood volume and involves relatively minor volume changes. The second type of response occurs as a result of prolonged increases of pressure and results in chronic distention of the vascular bed involving much larger volumes of blood. This phenomenon has been designated as "delayed compliance" by Alexander and Sarnoff and their associates and has been directly related to the prolonged maintenance of increased venous pressure.

Vascular hypertrophy which occurs in a limb after fracture is probably an example of "delayed compliance" on the part of the vascular bed of the entire limb. Although the problem requires additional study before complete clarification is obtained, certain changes occur in the circulatory environment after fracture of a limb which might reasonably be expected to contribute to enlargement of the vascular bed. Both the marked increase of blood flow into a limb which follows fracture of a long bone and the loss of functional muscle contraction as an aid to venous return would produce an increase in venous pressure. In addition, local p_H changes as a result of tissue damage probably contribute to vasodilation in the region of the fracture.

Progressive enlargement of the vascular bed of a limb after refracture suggests that the process is, for the most part, a passive phenomenon. Each manipulation would seem to set in motion the vasodilatory mechanism that produces further vascular bed enlargement with remarkable regularity. Recently, Judet has suggested that the hypervascularity observed around certain instances of nonunion is the cause of the nonunion. The observations made in this study lead to a different conclusion. It seems likely that the hypervascularity noted in some cases is the result and not the cause of the nonunion.

One interesting observation made during this experiment suggests that the initial stimulus leading to vascular bed hypertrophy may not be of bony origin. At the time of the first refracture, 9 days after the first fracture, union had not occurred and manipulation resulted in minimal bony disruption. In spite of this fact, further enlargement of the vascular bed of the limb developed. On the other hand, it seems reasonable that remanipulation probably pro-

duced further significant soft tissue and muscle damage and that a relationship exists between the soft tissue disruption and the factors leading to vessel enlargement.

The appearance of a marked increase in vascular volume after the third refracture, when union was quite firm, does not necessarily rule out the possibility of soft tissue origin to the stimulus as it might be reasoned that the more vigorous manipulation necessary at the third refracture would produce extensive soft tissue damage as well.

Extremely rapid union seemed to follow the third refracture, group D. A rapid drop in total vascular volume occurred in these limbs and this finding suggests that immobilization of the fracture inhibits or prevents the occurrence of the stimulus leading to vascular bed enlargement. However, the improved venous outflow which results from increased muscular activity in the limb undoubtedly plays a role and may be of even greater importance.

CONCLUSIONS

1. Closed fracture of the tibia in the rat leads to chronic enlargement of the vascular bed of the entire limb. This phenomenon is probably an example of "delayed compliance" which has been observed in other vascular beds.

2. Repeated refractures of the tibia lead to greater increases in vascular volume of the limb than those seen after a single fracture.

3. The characteristic increase in vascular volume occurs even when remanipulation of the fracture site is carried out in the absence of any bony union. Stimuli leading to vascular bed hypertrophy may arise from the soft tissues surrounding the fracture site.

REFERENCES

1. Alexander, R. S., Edwards, W. S., and Ankeney, J. L. The distensibility characteristics of the portal vascular bed. Circ. Res., 1953, 1: 271.
2. Judet, R. Nonunion of fractures. Presented at the 8th Congress of The International Society of Orthopaedics and Traumatology, Sept. 1960, New York City.
3. Lexer, E. Ueber die Ehtstehung von Pseudarthrosen nach Frakturen und nach Knochentransplantation. Arch. klin. Chir., 1922, 119: 520.
4. Sarnoff, S. J., and Berglund, E. Pressure-volume characteristics and stress relaxation in the pulmonary vascular bed of the dog. Amer. J. Physiol., 1952, 171: 238.
5. Wray, J. B., and Lynch, C. J. The vascular response to fracture of the tibia in the rat. J. Bone Surg., 1959, 41A: 1143.
6. Wray, J. B., and Spencer, M. P. The vasodilatory response to skeletal trauma. In press.

AN ANALYSIS OF ALTERATIONS IN BODY COMPOSITION IN BURNED PATIENTS

HARRY S. SOROFF, M.D., Brookline, Massachusetts,
ELINOR PEARSON, M.S., Fort Sam Houston, Texas,
GLEN K. ARNEY, M.D., San Francisco, California, and
CURTIS P. ARTZ, M.D., F.A.C.S., Jackson, Mississippi

ADEQUATE THERAPY for the severely burned patient includes the administration of large quanties of sodium. Colloid and electrolyte solutions containing sodium in amounts equal to one-fourth to one-third of the total exchangeable body sodium are administered during the first 72 hours to combat shock. However, after the first week the maintenance of an adequate intake of sodium in a moderate burn generally does not present a problem. The daily sodium balances are extremely positive in the immediate post-burn phase and become negative after 3 to 7 days, but the cumulative balance may remain positive well into convalescence.

During the balance periods of the current study (1, 5), the sodium intake was that which occurred naturally in the constituents of the formulas. The amounts per square meter per day for each plan are shown in Tables I and II. The primary importance of the sodium balances is in their relationship to the weight changes.

RESULTS

Balance data, plan I. Figures 1 and 2 show the sodium balances of patient 32 and control 32C. During period 1 all the patients had markedly negative cumulative balances (Table III). During the successive periods the change in magnitude and direction of the sodium balances showed great variation among the patients. The balances of 3 of the patients became progressively less negative or more positive, while the cumulative balances of the other 2 had no definite pattern. The controls had more positive sodium balances for the 10 day period than the patients had during any period.

Statistical analysis, plan I. Analysis of variance of the cumulative balances of each period showed that during periods 2 and 4 there was a statistically significant difference in the response of the patients to the total intake. There was no difference among the controls in the response to the total intake.

Since the exudate output of sodium varied among the patients, sodium balances of intake minus urinary output were also calculated and tested by analysis of variance. These balances were significantly different only for period 2.

An analysis of covariance to assess the effect of the previous day's intake on the balance indicated that the effect was not significant. The combined balances of each period were corrected for the regression due to the previous day's intake and a test for linearity performed on the regression of the adjusted balances on the intake. There was a significantly linear relationship in all patient-periods and for the controls (Figs. 3 and 4). The constants of the sodium regression lines are summarized in Table IV.

Balance data, plan II. The sodium balances of pair 2 who received the intermediate intake are shown in Figures 5, 6, 7, and 8. During period 1 the cumulative balances of the 6 patients were negative. The magnitude of the negativity varied greatly among the

From the U.S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas.

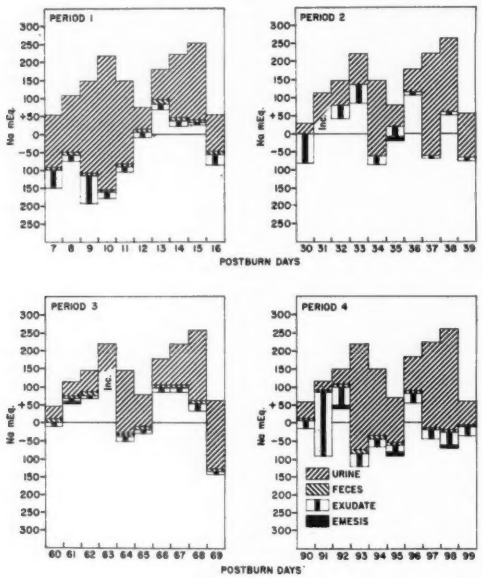


FIG. 1.

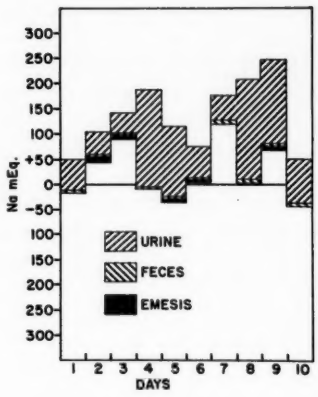


FIG. 2.

FIG. 1. Sodium balances of patient 32. The apparent large exudate loss on the second day of Period 4 is unexplained.

FIG. 2. Sodium balances of control 32C.

patients and did not appear to be directly related to the total intake (Table V). After period 1 the balances of patients 35, 36, 38, and 40 became less negative with each succeeding period, and by period 4 only the balance of patient 35 remained slightly negative. The 3 control pairs were in positive balance for the 10 days, the most sodium being retained by pair 3 on the highest intake.

TABLE I.—SODIUM INTAKE IN MILLIEQUIVALENTS PER SQUARE METER, PLAN I

Day of study	*Patient (and control)*				
	30	*31*	*32*	*33*	*34*
1	28	28	28	28	28
2	40	77	58	96	58
3	58	58	77	115	40
4	96	40	115	40	96
5	77	115	77	58	136
6	115	77	40	115	115
7	77	115	96	77	77
8	115	136	115	136	115
9	136	96	136	77	77
10	28	28	28	28	28

TABLE II.—SODIUM INTAKE IN MILLIEQUIVALENTS PER SQUARE METER, PLAN II

Day of study	*Patient (and control)*					
	Pair 1		*Pair 2*		*Pair 3*	
	35	*36*	*37*	*38*	*39*	*40*
1–5	40	96	58	115	77	136
6–10	96	40	115	58	136	77

Statistical analysis, plan II. The results of the analysis of variance of the sodium balance data are summarized in Table VI. The response to the total intake was significantly different during period 1 for pairs 2 and 3 and in period 2 for pairs 1 and 2. The level of intake had a significant effect on the balances of all 3 pairs of patients in period 1, for pairs 2 and 3 in period 3, and for pair 3 in period 4. There was a significant order-level interaction in 3 of the 12 comparisons, in period 1 of pair 3, in period 2 of pair 2, and in period 3 of pair 1. The only statistically significant finding in the 3 pairs of controls was in the response of pair 3 to the two levels of intake given.

Weight changes, plan I. The actual and theoretic weights of patient 32 and control 32C are shown in Figures 9 and 10. The solid lines are the observed weights and the broken lines the theoretic weights calculated from the nitrogen, sodium, and potassium balances by the method of Reifenstein. The theoretic weights indicate an estimation of the changes which have taken place in the protoplasm, extracellular fluid, and intra-

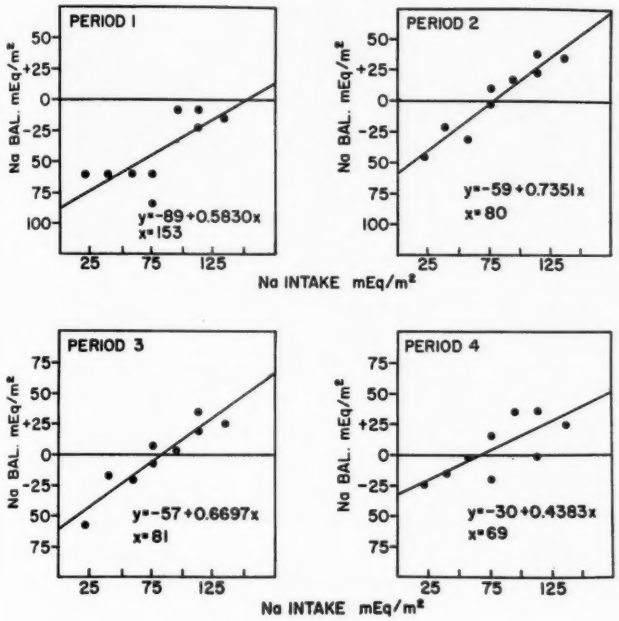


FIG. 3.

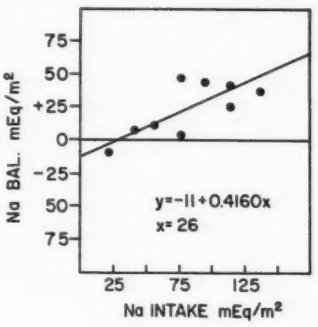


FIG. 4.

FIG. 3. Regression lines of the adjusted sodium balances of the patients in plan I. The combined balances of the 5 patients have been corrected for regression due to the effect of the previous intake. The lines are significantly linear.

FIG. 4. Regression lines of the adjusted sodium balances of controls in plan I.

cellular fluid during each 10 day period. The discrepancies between the two weight curves indicate a gain or loss of fat.

During period 1, 2 patients gained and 3 patients lost varying amounts of weight (Table VII), and a large discrepancy was observed between the observed and theoretic weights. After period 1 all of the patients gained during the study periods, but no consistent pattern of weight change existed. Only patients 33 and 34 had similar gains during each period. The actual and theoretic weight curves of all the patients showed better agreement as the postburn course progressed. In most instances, the actual weight curve was above the theoretic weight curve.

Most of the patients lost weight during the interval between study periods. Despite large weight gains during the study periods, only patient 34 weighed more than the reported preburn weight when period 4 ended. At that time the weight of patient 33 was only 0.9 kilogram less, but the other patients were from 6.0 to 12.0 kilograms under the preburn weight.

The controls gained from 1.3 to 5.0 kilograms during the 10 day study period. Only controls 32C and 33C had greater gains than their partner-patient during period 4. Early in the period the actual weight curves were above the theoretic, and the positions were reversed in the latter part of the period.

TABLE III.—TOTAL CUMULATIVE SODIUM BALANCES IN MILLIEQUIVALENTS, PLAN I

	Patient (and control)				
Period	*30*	*31*	*32*	*33*	*34*
1	−517*	−965	−657	−1041	−617
2	+561	−125	+117	−270	−296
3	−360	+ 79	+ 74	+ 55	−197
4	+ 46	+241	−464	+393	+ 32
Controls	+426	+277	+221	+682	+327

*Six days.

TABLE IV.—CONSTANTS OF REGRESSION LINES OF ADJUSTED SODIUM BALANCES, PLAN I

Period	*x-intercept*	*y-intercept*	*Slope*
1	153	−89	0.5830
2	80	−59	0.7351
3	65	−44	0.6697
4	69	−30	0.4383
Controls	26	−11	0.4160

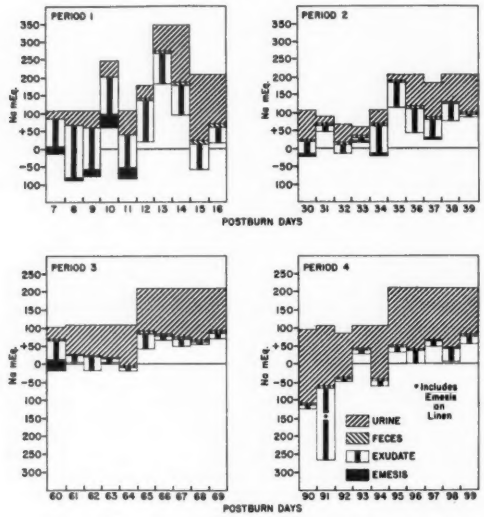


FIG. 5.

FIG. 5. Sodium balances of patient 37, pair 2. This patient was given 105 milliequivalents of sodium during the first 5 days of each period and 207 milliequivalents during the last 5 days. On the fourth, seventh, and eighth days of period 1 a liter of polysol containing 140 milliequivalents of sodium was given intravenously. There were from 1 to 4 days of incomplete intake during each period. On day 2 of period 4 emesis losses on the linen were included with the exudate. The stool specimen of both periods 2 and 4 were analyzed also as 10 day samples.

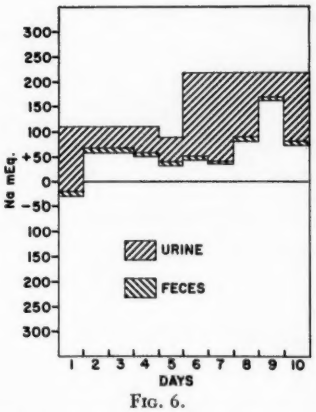


FIG. 6.

FIG. 6. Sodium balances of control 37C, pair 2. This control was given a total daily intake of 110 milliequivalents during the first 5 days of the period and 218 milliequivalents during the last 5 days. On the fifth day intake was incomplete.

Weight changes, plan II. Figures 11, 12, 13, and 14 show the weight curves of pair 2 (Table VIII). During period 1 both patients of pair 1 lost weight, 1 patient of pair 2 lost, while both members of pair 3 gained weight. Agreement between the actual and theoretic weight curves was poor.

During period 2 only 1 patient lost weight, while the other 5 gained varying amounts. However, the weight changes of the members of each pair differed during subsequent periods. The members of pair 1 had greater gains on the lower nitrogen intake, and the members of the other 2 pairs had greater gains on the higher nitrogen intake. The actual and theoretic weight curves showed better agreement in the later periods. The members of each pair who received the lower nitrogen intake first had the actual weight curve above the theoretic curve. The positions of the weight curves were reversed for those who received the higher nitrogen intake first.

All of the patients lost weight between the study periods with the exception of patient 36 who gained 0.5 kilogram between periods 2 and 3 and patient 39 who gained 0.5 kilogram between periods 3 and 4. However, at the end of period 4 the weights were still from 3.3 to 11.9 kilograms less than the reported preburn weights.

The controls all gained weight during the study period, and the magnitude of the changes differed from those of the partner-patient during period 4. Two controls had greater gains, while 4 gained less than the patients. The actual weight curve was above the theoretic weight curve when the lower nitrogen intake was given first and below when it was given last.

DISCUSSION

Sodium metabolism is generally considered in its relation to water metabolism. The first 24 to 72 hour period of the postburn course is characterized by the requirement for large amounts of sodium and colloid solutions. The formula recommended by

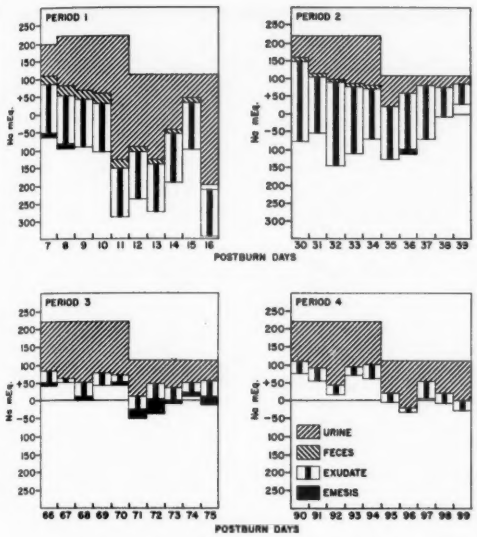


FIG. 7.

FIG. 7. Sodium balances of patient 38, pair 2. This patient was given a total daily intake of 218 milliequivalents for the first 5 days of each period, and 110 milliequivalents for the last 5 days. On the first day of period 1 the intake was incomplete. On the low intake of period 2 and both levels of periods 3 and 4 the fecal sodium was a negligible part of the output.

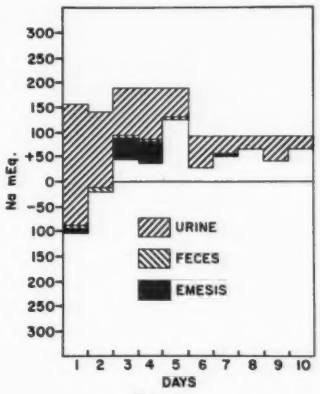


FIG. 8.

FIG. 8. Sodium balances of control 38C, pair 2. This control was given a total daily intake of 184 milliequivalents for the first 5 days of the period and 93 milliequivalents for the last 5 days. On the first and second days the intake was incomplete. The fecal sodium was a negligible part of the output on the low intake.

Reiss and Artz (4) for resuscitation of burned patients was used as a guide in the treatment of the patients in this study. During the immediate postburn period there is retention of sodium and water in the edema fluid. If resuscitative therapy is satisfactory and no complications occur, the burned patient will begin to excrete both more sodium and water in the urine between the fourth and sixth postburn days. This is reflected by the large urinary sodium output observed in most of the patients during period 1. The administration of glucose and water with resultant large urinary volumes may have contributed to the natruresis.

The exudate contribution to the total sodium output was large during periods 1 and 2. Gauze pads used on the wound surface to hasten the separation of the eschar and to keep the granulating wounds clean were moistened with distilled water since exudate sodium was to be measured. The distilled water apparently set up an osmotic gradient between the wound surface and the environment, permitting excessive amounts of sodium to pass from the granulations into the dressings. If known amounts of a physiologic solution had been used, the sodium losses in the exudate would have been more representative of the obligatory loss from this route.

In general, the sodium balances became less negative or more positive as the postburn course progressed. However, if the exudate sodium is ignored and balances are calculated from sodium intake minus urinary sodium, the patients would have been in positive balance during all periods. The controls in both plans had more positive sodium balances than did their partner-patients during period 4. No attempt was made to determine sweat losses in either the patients or controls, and the patients' dressings may have contained some sodium from this source. The controls were studied during the summer months and were allowed limited activities outside the air-conditioned ward.

More variation existed among the patients in response to the total sodium intake than

TABLE V.—TOTAL CUMULATIVE SODIUM BALANCES IN MILLIEQUIVALENTS FOR EACH LEVEL OF INTAKE, PLAN II

Patient	*Intake*	*Period* 1	2	3	4	*Controls*
Pair 1						
35	39	−1146	− 74	+164	− 50	+156
	98	− 586	− 40	−215	+ 26	+221
	Total	−1732	−114	− 51	− 24	+377
36	98	− 746	−632	−135	+128	+201
	39	− 912	−313	−106	− 28	+143
	Total	−1658	−945	−241	+100	+344
Pair 2						
37	58	− 208	+ 17	− 51	−473	+180
	115	+ 256	+351	+282	+140	+412
	Total	+ 48	+368	+231	−333	+592
38	115	− 638	−451	+176	+275	+ 91
	58	−1153	−288	− 86	− 71	+253
	Total	−1791	−739	+ 90	+204	+344
Pair 3						
39	76	− 146	−379	−256	− 95	+244
	138	− 50	− 35	−258	+ 44	+581
	Total	− 196	−414	−514	− 51	+825
40	138	+ 179	−123	+ 9	+210	+486
	76	−1014	+ 7	− 94	+ 65	+284
	Total	− 835	−116	− 85	+275	+770

TABLE VI.—ANALYSIS OF VARIANCE OF SODIUM BALANCES, PLAN II

	Pair 1			*Pair 2*			*Pair 3*		
Period	*Patient (order)*	*Level of intake*	*Interaction*	*Patient (order)*	*Level of intake*	*Interaction*	*Patient (order)*	*Level of intake*	*Interaction*
1	N.S.	4.76*	N.S.	14.30†	9.40*	N.S.	6.67*	25.27‡	18.89‡
2	12.50†	N.S.	N.S.	31.07‡	N.S.	6.35*	N.S.	N.S.	N.S.
3	N.S.	6.73*	4.64*	N.S.	54.63‡	N.S.	N.S.	N.S.	N.S.
4	N.S.	N.S.	N.S.	N.S.	13.89†	N.S.	N.S.	N.S.	N.S.
Controls	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	10.27†	N.S.

*Significant at 5.0 per cent level.
†Significant at 1.0 per cent level.
‡Significant at 0.1 per cent level.

to either the nitrogen or potassium intake. The difference was statistically significant during periods 2 and 4 of plan I and the first 2 periods of plan II. Another indication of the difference in response was the infrequency of periods in plan I in which the balances of the individual patients showed a linear relationship to the intake in contrast to the nitrogen and potassium data which were consistently linear. However, the adjusted sodium balances of plan I and the combined data of periods 1 and 4 of plan II showed a linear relationship. The adjusted balances of the controls of plan I and the combined balances of the controls of plan II were linear.

The constants of the sodium regression lines of the 4 periods of plan I became smaller with each successive period. It is of interest that patients on an ad libitum intake in a previous study (3) voluntarily consumed quantities of sodium similar to those suggested as necessary for equilibrium by the x-intercepts of periods 3 and 4 of plan I. However, a too literal interpretation of the significance of the sodium regression lines is not warranted since under normal circumstances an adequate intake of sodium is easily maintained.

It was expected that the patients would gain weight during the study periods because of the high caloric intake. During period 1 only 5 of the 11 showed an increase in weight. Weight changes during period 1 represent more than a change in lean body mass and fat. During this period the loss of weight might well represent the mobilization and excretion of fluid sequestered in the burn wound during the immediate postburn phase. Conversely, the retention of fluid and

TABLE VII.—WEIGHT CHANGES IN KILOGRAMS, PLAN I

	Patient (and control)				
Period	*30*	*31*	*32*	*33*	*34*
1	+1.6*	+0.3	−2.3	−4.1	−0.6
2	+8.6	+0.4	+2.4	+3.6	+3.9
3	+6.4	+5.3	+6.4	+3.8	+2.9
4	+5.5	+7.5	+4.1	+3.0	+3.2
Controls	+2.7	+4.1	+5.0	+4.1	+1.3

*Six days.

TABLE VIII.—WEIGHT CHANGES IN KILOGRAMS FOR EACH LEVEL OF INTAKE, PLAN II

		Period				
Patient	*Intake*	*1*	*2*	*3*	*4*	*Controls*
Pair 1						
35	Low	−7.3	+4.3	+7.0	+4.1	+2.3
	High	+0.4	+1.9	−0.2	+1.9	+2.4
	Total	−6.9	+6.2	+6.8	+6.0	+4.7
36	High	−1.8	−1.8	−3.4	+2.7	+1.6
	Low	−5.9	−1.9	+4.8	+2.7	+0.2
	Total	−7.7	−3.7	+1.4	+5.4	+1.8
Pair 2						
37	Low	+3.6	+1.4	+1.1	+1.9	+3.3
	High	+1.4	+2.7	+3.0	+2.9	+2.2
	Total	+5.0	+4.1	+4.1	+4.8	+5.5
38	High	−3.0	+3.4	+4.5	+5.6	+2.0
	Low	−8.0	−1.3	+0.7	+1.8	+0.9
	Total	−11.0	+2.1	+5.2	+7.4	+2.9
Pair 3						
39	Low	+0.1	−3.2	+0.2	+6.3	+1.8
	High	+1.5	+3.9	+2.6	−0.1	+0.7
	Total	+1.6	+0.7	+2.8	+6.2	+2.5
40	High	+9.2	+2.9	+2.1	+2.7	+3.9
	Low	−4.0	+2.1	0	+0.4	+2.3
	Total	+5.2	+5.0	+2.1	+3.1	+6.2

sodium would result in a gain in weight. During periods 2, 3, and 4 all patients gained weight. However, there was no quantitative correlation between the amount of weight gained and the amount of nitrogen, sodium, and potassium stored.

Theoretic weight curves calculated from the nitrogen, sodium, and potassium balances estimate the changes in protoplasm, extracellular fluid, and intracellular fluid. The discrepancies between the actual and the theoretic weight curves are interpreted as a change in body fat: a gain of fat when the actual weight curve is above the theoretic weight curve and a loss of fat when it is below. Because the interpretation is valid only if the same state of hydration exists at the beginning and end of the period being considered, no estimate of body fat changes can be made from the weight curves of period 1.

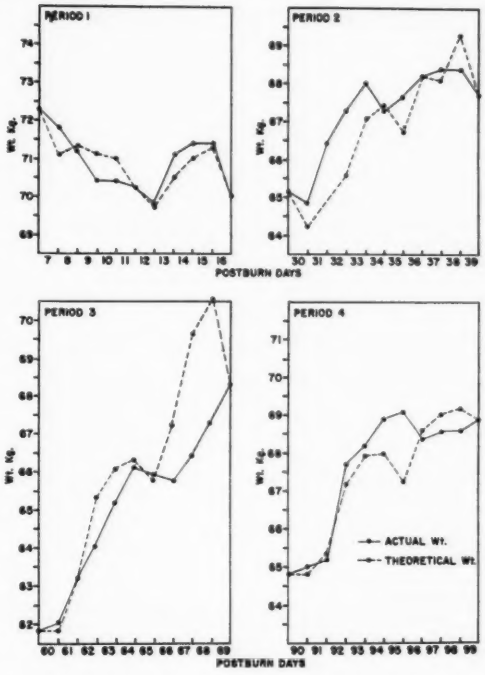


FIG. 9.

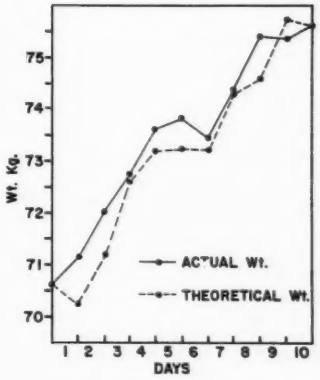


FIG. 10.

FIG. 9. Weight curves of patient 32.
FIG. 10. Weight curves of control 32C.

Theoretic weight curves were calculated by using sodium balances based on intake minus only urinary sodium in order to ascertain the effect of the unusually high losses found in the exudate. The relative positions of the theoretic and observed

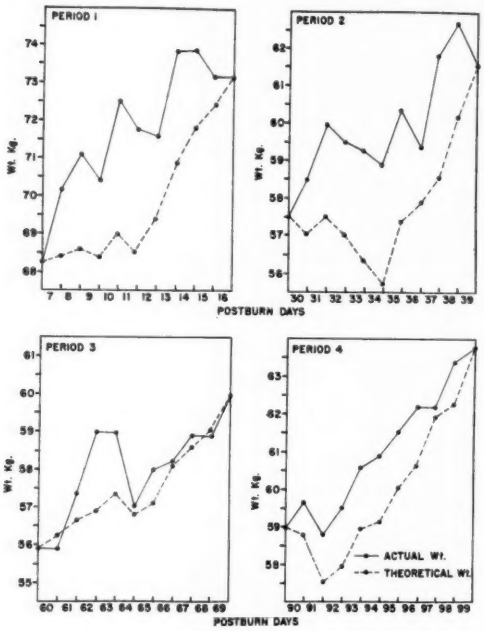


FIG. 11.

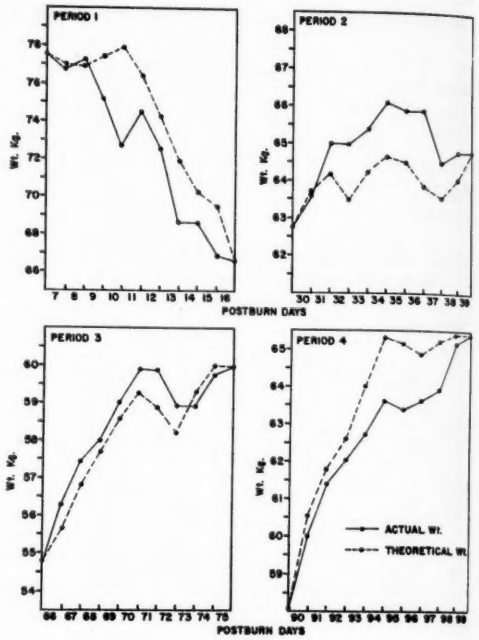


FIG. 13.

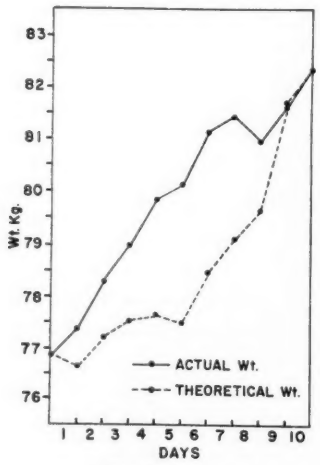


FIG. 12.

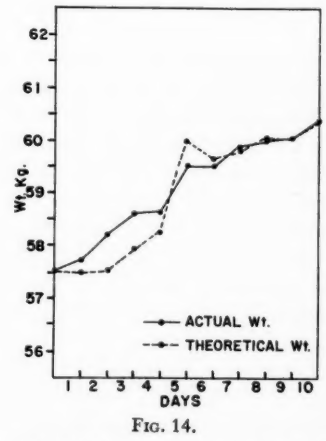


FIG. 14.

FIG. 11. Weight curves of patient 37, pair 2.
FIG. 12. Weight curves of control 37C, pair 2.

FIG. 13. Weight curves of patient 38, pair 2.
FIG. 14. Weight curves of control 38C, pair 2.

weight curves were only slightly altered (Fig. 15).

A comparison of the actual and theoretic weight curves of periods 2 and 4 of plan I showed fat storage early in the period and fat loss during the last 2 or 3 days. The immediate depression in the theoretic weight curve is a reflection of the temporarily nega-

tive balances on a day of high calorie, "zero" nitrogen intake. On the last day of the periods, the sudden removal of all except carbohydrate and fat calories caused either a decrease in the rate of actual gain or a slight weight loss. It would appear that the high caloric intake was sufficient to support anabolism and to initiate storage of fat, but after 7 or 8 days on the intake it was necessary to utilize some of the stored fat in order to maintain the anabolic processes.

During period 3 the positions of the two curves were reversed, and the theoretic weights were generally greater than the actual weights. Clinically, period 3 was a characteristic turning point in the postburn course. The wounds were essentially healed and no longer had priority in the metabolic scheme. The lowest postburn weights were observed at the beginning of this period, suggesting maximal depletion of lean body mass and fat depots and minimal reserves. Conditions were ideal for the active replacement of lost tissues. Although the study intake was sufficient to cause a large weight gain and positive balances, on many days the theoretic weight curves indicated a loss of fat. It would appear that more energy was required to support both protein synthesis and the storage of fat than was furnished by the intake. Therefore, it can be postulated that the ability of the anabolic processes to function maximally is limited only by the inability to furnish the calories necessary for energy purposes.

Although the absolute weight gains of the controls of plan I were not the same as those of the patients during period 4, the relationship in the weight curves was similar: the actual weight was greater than the theoretic weight during the early part of the period and less during the latter part. Initially, the intake caused a more rapid increase in fat than lean tissue. Later, the fat was required to support the continuing anabolism.

In plan II the patient of pair 1 who received the low nitrogen intake first consistently had a greater weight gain on the low intake during periods 2, 3, and 4. The relative positions of the two weight curves indicated that the greater gain was not only attributable to an increase in protoplasm and intracellular and extracellular fluids but also to an increase in fat. Since the intake was isocaloric and the fat content was constant, the intake with the least amount of nitrogen contained the most calories as carbohydrate. The caloric intake was more than adequate to support anabolism of the lower level of nitrogen administered, and the excess calories were stored as fat. The higher nitrogen intake apparently required the utilization of some of the stored fat, since after the intake changed both the rate of gain and the difference between the two weight curves diminished. The other member of the pair who received the high intake first lost fat on

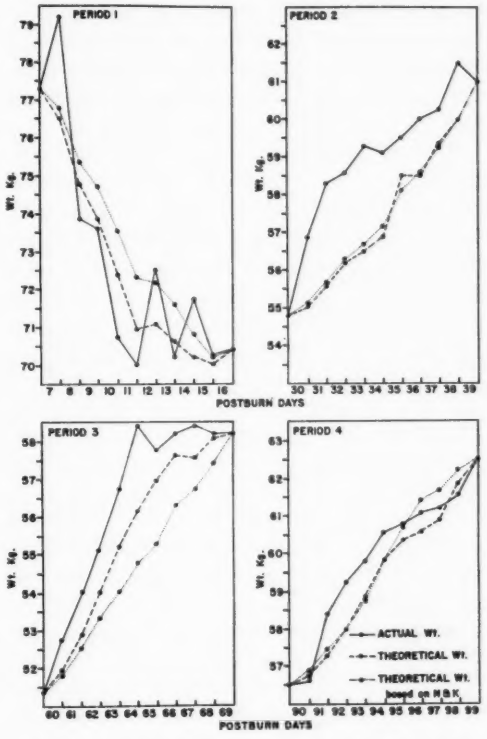


FIG. 15. Weight curves of patient 35. The nitrogen, sodium, and potassium balances used in calculating the theoretic weight curves were determined from intake minus urinary output.

both levels of intake during all periods. The administration of the higher nitrogen intake first with its smaller per cent of carbohydrate calories obscured the deposition of fat noted in each period of the partner-patient.

During periods 2, 3, and 4 the other two pairs of patients had the greatest weight gain while receiving the higher nitrogen intake. A consistent, clear-cut relationship between the actual and the theoretic weight curves was not apparent in these 2 pairs until period 4. In period 4 the pattern was the same as that seen in all periods of pair 1. The members of pairs 2 and 3 who received the low nitrogen intake first gained fat throughout the period, and the member who received the high nitrogen intake first lost fat.

The actual and theoretic weight curves of the 3 pairs of controls also indicated a gain of fat by the member who received the low intake first and a loss of fat by the member who received the high intake first. The weight changes of all the controls and patients of pair 1 were similar in that the intake with the larger per cent of calories from carbohydrate initiated the storage of fat which continued throughout the period.

During period 4, 7 of the 11 patients had greater weight gains than their controls. At the beginning of this period, the weight of the patients was less than the reported preburn weight except for patient 34. Since the patient intake for all study periods was based on the surface area determined from the height and preburn weight, only patient 34 had an area equal to his preburn surface area at the beginning of period 4. The other patients had a surface area from 0.1 to 0.3 square meter less. As a result the patients received a relatively larger intake than the controls.

SUMMARY

By inspection there is not an obvious relationship between the magnitude of the weight changes and the nitrogen, potassium, and sodium balance data. However, calculations of theoretic weight curves from these data show good agreement between the observed and the theoretic weight changes. It is not possible to interpret weight changes as changes in lean body mass and fat during period 1 because of the changing state of hydration during this interval of the postburn course. The patients in plan I stored fat and protein during periods 2 and 4 and were catabolizing fat in the presence of lean tissue gain during period 3. Presumably the caloric intake was inadequate during this period of active protein synthesis, and additional calories were obtained from the endogenous fat stores.

The order of the administration of the high nitrogen intake had an apparent influence on the changes in fat storage of the patients in plan II. When the low nitrogen intake was given first, it was accompanied by a higher carbohydrate intake, and fat was stored throughout the period; but when the low nitrogen intake was given last, fat was lost during the entire period. This phenomenon was most striking in all periods of pair 1, in period 4 of pairs 2 and 3, and in the controls. It is suggested that during certain periods of the postburn course anabolism of protein has priority so that stored fat may be utilized to further protein synthesis and storage.

REFERENCES

1. Pearson, E., Soroff, H. S., Arney, G. K., and Artz, C. P. An estimation of the potassium requirements for equilibrium in burned patients. Surg. Gyn. Obst., 1961, 112: 263–273.
2. Reifenstein, E. C., Jr., Albright, F., and Wells, S. L. The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. J. Clin. Endocr., 1945, 5: 367–395.
3. Reiss, E., Pearson, E., and Artz, C. P. The metabolic response to burns. J. Clin. Invest., 1956, 35: 62–77.
4. Reiss, E., Stirman, J. A., Artz, C. P., Davis, J. H., and Amspacher, W. H. Fluid and electrolyte balance in burns. J. Am. M. Ass., 1953, 152: 1309–1313.
5. Soroff, H. S., Pearson, E., and Artz, C. P. An estimation of the nitrogen requirements for equilibrium in burned patients. Surg. Gyn. Obst., 1961, 112: 159–172.

INTERVILLOUS BLOOD OXYGEN STUDIES

WILLIAM F. HOWARD, M.D., CHARLES A. HUNTER, JR., M.D.,
and CARL P. HUBER, M.D., Indianapolis, Indiana

THE INACCESSIBILITY of the human fetal vessels has prevented the direct study of fetal oxygenation in utero. However, a study of fetal oxygenation can be approached at present by an indirect method, i.e., a study of the oxygen delivered to the placenta by the maternal circulation. This study can be carried out readily on samples of the intervillous space blood obtained by transabdominal uterine puncture.

The oxygen content and saturation of the human intervillous blood have been measured previously by Prystowsky (5, 6). These results were based upon samples of blood which were obtained during the second stage of labor when delivery was imminent and, therefore, they represent only a limited period of study.

The objectives of the present study are twofold: (1) determination of the intervillous oxygen saturation during the last trimester of pregnancy in both the normal and the pre-eclamptic patient and (2) evaluation of the effect of myometrial contraction upon oxygen saturation levels in this space.

MATERIAL AND METHODS

This report is based upon the observation of 74 clinic patients. Intervillous taps were performed, from the twenty-eighth to the fortieth week of pregnancy, in a manner similar to that described by McGaughey and his colleagues. The skin and peritoneum were infiltrated with 1 per cent xylocaine. A No. 18 gauge spinal needle was then inserted through the abdominal wall and uterus until a free flow of blood occurred from the intervillous space. The blood was collected in oiled 2 milliliter syringes which had been rinsed previously with sodium oxalate, immediately capped with mercury, and placed on ice. All determinations were made within an hour of the time that the samples were collected.

The oxygen content and capacity were determined by the method of Roughton and Scholander. The percentage saturation was calculated by dividing the oxygen content by the oxygen capacity and multiplying by 100:

$$\frac{O_2 \text{ content}}{O_2 \text{ capacity}} \times 100 = \text{per cent saturation}$$

In 10 patients with uncomplicated term pregnancies, oxygen determinations were made during spontaneous labor in the same manner as that previously described, with the exception that the needle was held in place manually and repeated intervillous blood samples were obtained before, during, and after uterine contractions. One hundred per cent oxygen was then administered to these patients by means of a face mask for a period of at least 5 minutes and then another intervillous blood specimen was obtained.

Every patient studied in these series was delivered of a normal living fetus. There were no cases of clinical fetal distress and no neonatal deaths.

RESULTS

The mean oxygen saturation of intervillous blood from normal patients in three parity groups is seen in Table I. The oxygen saturation varied from 39.5 to 88.8 per cent. The oxygen saturation of the three parity groups was remarkably constant, measuring 69.26, 69.57, and 69.29 per cent for a mean of 69.35 per cent.

The oxygen saturation of intervillous

From the Department of Obstetrics and Gynecology, Indiana University Medical Center and Marion County General Hospital, Indianapolis, Indiana.

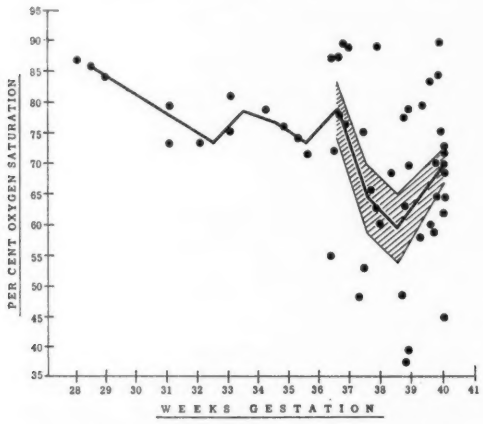


FIG. 1. Oxygen saturation of intervillous blood from normal patients not in labor plotted according to number of weeks of gestation.

blood from patients with pre-eclampsia is seen in Table II. The mean oxygen saturation of this group was 53.80 per cent, which is significantly lower than the mean value recorded for the normal patients ($p<0.01$). The range of oxygen saturation prior to treatment was 40.7 to 65.4 per cent in this group.

TABLE I.—INTERVILLOUS BLOOD OXYGEN SATURATION DURING LAST TRIMESTER OF NORMAL PREGNANCIES

Parity	*No. of patients*	*Saturation, per cent*	*Range, per cent*
0	20	69.26	39.5–88
I	15	69.57	35.5–86.2
II+ ↑	23	69.29	46.1–88.8

TABLE II.—INTERVILLOUS BLOOD OXYGEN SATURATION IN PRE-ECLAMPTIC PATIENTS

Pt.	*Date*	*O_2 content*	*O_2 capacity*	*Saturation, per cent*
1	2-5	5.92	11.43	51.1*
	2-18	6.88	11.07	61.2†
2		6.13	9.93	60.7
3		8.96	15.17	58.5
4		9.93	15.02	65.4
5		7.86	19.13	40.7
6	1-22	6.33	13.65	46.4*
	1-24	8.86	15.73	55.8†
	1-30	10.61	16.27	64.6†

*Before treatment.
†After treatment.

As indicated in Figure 1, the oxygen saturation of intervillous blood from normal patients not in labor is plotted according to the number of weeks of gestation. Prior to 36 weeks' gestation, the oxygen saturation varied from 73 to 87 per cent. The mean oxygen saturation prior to 36 weeks' gestation was 78.1 per cent. The mean saturation from 36 to 40 weeks of gestation was 66.3 per cent. The standard error is illustrated in the graph.

In Figure 2, the mean oxygen saturation levels of 10 patients in labor is demonstrated. Immediately before a myometrial contraction, the intervillous blood was 69 per cent saturated. During a contraction, the mean saturation fell to 54 per cent. Immediately after a contraction, the saturation rose to 74 per cent. The administration of oxygen to these patients elevated the mean saturation of intervillous blood from 74 to 83 per cent.

DISCUSSION

The intervillous space is unique in that there is direct mixing of arterial and venous blood. It could be designated as an "acquired physiologic arteriovenous fistula." The oxygen saturation of the blood in this space depends upon three factors: (1) the oxygen saturation of the arterial blood delivered to this space, (2) the volume of blood delivered per unit of time, and (3) the amount of oxygen transferred across the placental villous surface. A reduction in oxygen saturation, therefore, could be due to inadequate saturation of the arterial blood in the pulmonary parenchyma, a relative decrease in or inadequate uterine blood flow, or increased oxygen transfer across the placental surface.

The wide range of saturation levels in normal pregnancies makes one wonder whether thorough mixing of the arterial and venous blood occurs in this space. However, McGaughey and his colleagues have demonstrated indirectly the reliability of this mixing by injecting a foreign material into the peripheral circulation and demonstrat-

ing identical quantities in different sites within the intervillous space.

The oxygen saturation levels in the intervillous space of pre-eclamptic patients were lower than the oxygen saturation values in normal patients. This difference is highly significant when analyzed statistically. In toxemia of pregnancy the intervillous oxygen saturation values are uniformly low and less variable than the oxygen saturation values in normal pregnancies. This is in accord with the experience of Browne, Moore, Morris, and Weis and their associates who have demonstrated decreased uterine blood flow in toxemia by utilizing radioactive sodium uptake studies. The increase in the oxygen saturation levels in 2 pre-eclamptic patients who were treated conservatively by bedrest and diuretics demonstrates the effectiveness of this type of treatment in the correction of the primary pathophysiologic process of this disease, i.e., hypoxia.

A statistical analysis of the relationship of oxygen saturation to the number of weeks of gestation would require a much larger number of patients than that reported herein. However, low saturation levels are nonexistent until the thirty-sixth week of gestation is reached, at which time the range increases markedly. The "low" saturation levels must represent either a decrease in uterine blood flow as the uterus distends or an increase in the utilization of oxygen by the fetus.

The intervillous blood oxygen saturation levels are lowered temporarily during a myometrial contraction. A reduction occurs in the saturation levels as the myometrial contraction begins and the levels are inversely proportional to the intensity and length of the contraction. This is probably due to impeded drainage with a relative increase in the amount of venous blood in the intervillous space. Immediately after relaxation of the myometrium, an outpouring of venous blood occurs and the ratio is then reversed so that there is a relative increase in the amount of arterial blood which is present within the intervillous space.

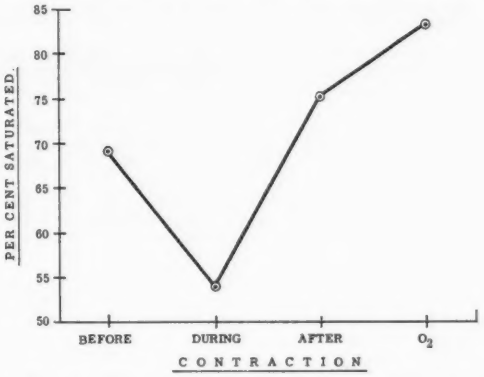


FIG. 2. Mean oxygen saturation levels of intervillous blood of 10 patients in labor.

The administration of oxygen to a woman in labor elevated the oxygen saturation of the intervillous blood in every case. The exact mechanism of this phenomenon is unknown. The values obtained in preliminary studies of the arterial oxygen saturation in women in labor are below those accepted as normal. This would tend to point toward defective pulmonary oxygenation in these patients.

SUMMARY

1. The mean oxygen saturation of intervillous blood from normal patients during the last trimester of pregnancy was 69.4 per cent. The mean oxygen saturation value of blood from pre-eclamptic patients was 53.8 per cent, which is a significantly lower value.

2. The intervillous blood oxygen saturation values are lowered temporarily during myometrial contractions. This reduction is inversely proportional to the intensity and duration of the contraction.

3. The administration of oxygen to a patient in labor elevates the oxygen saturation of intervillous blood.

4. In this series there appears to be a decrease in the per cent of oxygen saturation as term approaches.

REFERENCES

1. Browne, J. C. M., and Veal, N. The maternal placental blood flow in normotensive and hypertensive women. J. Obst. Gyn. Brit. Empire, 1953, 60: 142.
2. McGaughey, H. S., Jr., Jones, H. C., Jr., Talbert, L., and Anslow, W. P., Jr. Placental transfer in normal and toxic gestation. Am. J. Obst. Gyn., 1958, 75: 482.
3. Moore, P. T., and Myerscough, P. R. Clearance rates of radiosodium from myometrium. J. Obst. Gyn. Brit. Empire, 1957, 64: 207.
4. Morris, N., Osborn, S. B., and Wright, H. P. Effective circulation of the uterine wall in late pregnancy. Lancet, Lond., 1955, 1: 323.
5. Prystowsky, H. Fetal blood studies—VII. Bull. Johns Hopkins Hosp., 1957, 101: 48.
6. Idem. A report of fetal blood studies. Obst. Gyn., 1958, 12: 164.
7. Roughton, F. J. W., and Scholander, P. F. Microgasometric estimation of the blood gases. J. Biol. Chem., 1943, 148: 3.
8. Weis, E. B., Jr., Bruns, P. D., and Taylor, E. S. Disappearance of $Na^{22}Cl$ from myometrium. Am. J. Obst. Gyn., 1958, 76: 340.

COMMON VARIATIONS IN RENAL ANATOMY, AFFECTING BLOOD SUPPLY, FORM, AND TOPOGRAPHY

BARRY J. ANSON, Ph.D.(Med.Sc.), Chicago, Illinois, and
EDWARD H. DASELER, M.D., Pomona, California

IN AN EARLIER REPORT (3) it was pointed out that the variations in the pattern of the renal vessels are of such common occurrence that many of them are represented in any small, unselected group of dissections. This range in variation of the pattern of renal and related blood supply has now been studied in a consecutive series of 100 cases. To the observations on vascular supply have been added the results of study of renal topography and the positional relations of the arteries and veins in the renal pedicle.

In several earlier publications, it has been repeatedly stressed that the simple form of the renal pedicle, as portrayed in standard anatomic texts, occurs in less than one-fourth of the cases critically studied in the laboratory. In the present article, our purpose is to demonstrate further the range of these variations, forming a perfectly graded series from the simple to the exceptional, to record observations on topographic relations to skeletal landmarks, and to discuss the surgical significance of the several types of variation.

MATERIAL AND METHODS

For the present article and for the two which preceded it, 100 specimens have been examined consecutively and drawings made of both the common and the unusual variations encountered. In 125 specimens, the variations in relationship of the renal arteries and veins and in 30, the length of the venous pedicle were recorded. Finally, in more than 235 of the bodies examined, the relations of the superior and inferior extremities, upper and lower poles, to vertebral and pelvic bony landmarks have been recorded and graphically illustrated.

In the combined lot of 100 consecutive specimens, the following striking variations in renal venous pattern were encountered on the left side: independent termination of the suprarenal vein, that is, not as a confluent stem with the inferior phrenic; doubling of the suprarenal; division of the renal into preaortic and retroaortic limbs, with an internal spermatic tributary to each; separate renal termination of the second lumbar and the internal spermatic veins; similar ending for third lumbar and the spermatic; division of the internal spermatic; local splitting midcourse of the renal vein with passage of the internal spermatic artery through the hiatus; renal termination of capsular veins; late junction of renal arms of the single vein, with termination of the internal spermatic in the ventral segment and the third lumbar vein in the dorsal segment; confluence of the internal spermatic and the suprarenal to form a common tributary to the renal.

VERTEBRAL RELATIONS

The normal kidneys are regularly described as being situated opposite the twelfth thoracic, or dorsal, and the first three lumbar vertebrae. To this "typical" relationship there are many exceptions. Figure 1 shows in modified graphs the relationships of the upper and lower renal poles to the vertebral bodies and intervertebral discs. In 16 cases of a total of 194 on the left side and in 12 cases of 193 on the right side, the superior extremity extended above the level of the

Contribution No. 652 from the Department of Anatomy, Northwestern University Medical School, Chicago. This is the third in a series on renal vascular anatomy published in this Journal (3, 7).

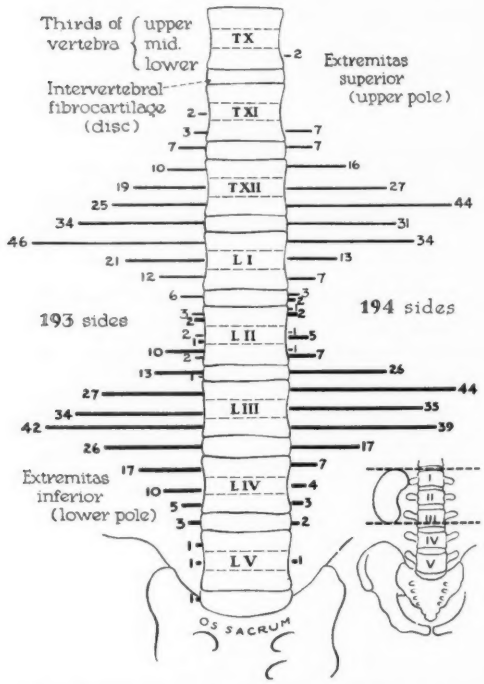


FIG. 1. Frequency graph to record the levels of the superior and inferior extremities of kidney, upper and lower renal poles, in relation to vertebral bodies and intervertebral disc spaces. Each of the vertebral bodies has been divided into upper, middle, and lower thirds. The levels for the superior renal extremity are indicated by means of thin lines, those for the inferior are shown by broad lines.

twelfth thoracic vertebra. Despite this fact, no example of intrathoracic kidney was encountered. However, Robbins and Lich found reports of 10 cases of intrathoracic kidney in the literature, to which they added a case of their own. In a review of 13,000 autopsies, Spillane and Prather encountered a single example of intrathoracic kidney, which attests to the rarity of this anomaly. In a far greater number of specimens, 34 on the left and 64 on the right side, the lower renal poles were stationed below the "standard level," that is, the lower border of the third lumbar vertebra. This study also illustrates a definite tendency of the right kidney to be situated at a level inferior to that of the left. However, the reverse arrangement may exist: McClellan, in a study of 1,500 excretory pyelograms, found the left kidney to be lower than the right in 106 cases, or 7.1 per cent—the low position being attributable, in some instances, to disease.

The relationship of the superior and inferior extremities of the kidneys to the readily palpable iliac crests likewise present wide variation in positioning (Figs. 2 and 3).

Another clinically important landmark, of course, is the sacral promontory. The distance between the promontory and lower renal extremity was measured in 232 bodies (Fig. 4). The range is again one of considerable magnitude, from 4.25 to 15.5 centimeters, with the majority of lower renal poles being situated at a level of from 9.5 to 11.5 centimeters above or cranial to the sacral promontory.

Measurements were next made of the distance in centimeters between the outer convex borders of the kidneys (Fig. 5). The distances varied from 14.75 to 23.35 centimeters, with an average distance of approximately 19 centimeters. It is clear, then, that the location of normal kidneys varies in both the vertical and the horizontal directions.

Accompanying variations occur in the positions of the bony landmarks themselves, in relation to one another. For example, the relation of vertebral bodies to iliac crests shows a range of variation of slightly more than 2 vertebral bodies and 3 intervertebral discs (Fig. 6).

An even greater difference is observed in the distance between the sacral promontory and the levels of the iliac crests (Fig. 7). It seems likely that part of the variation encountered in renal positioning is the result of differences in position of the bony anatomic landmarks used to determine the location of the kidneys.

VASCULAR RENAL PEDICLE

The structural pattern of the renal veins is to a great extent governed by the length of the respective vessels of the right and left sides, since the regions crossed by each vessel play a major role in determining both the

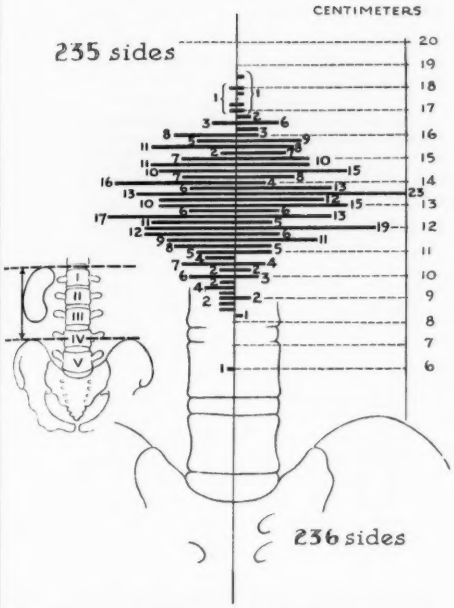


FIG. 2. Graphic record of the relationship between the superior renal extremity and the iliac crests. Approximate range is 6 to 18 centimeters.

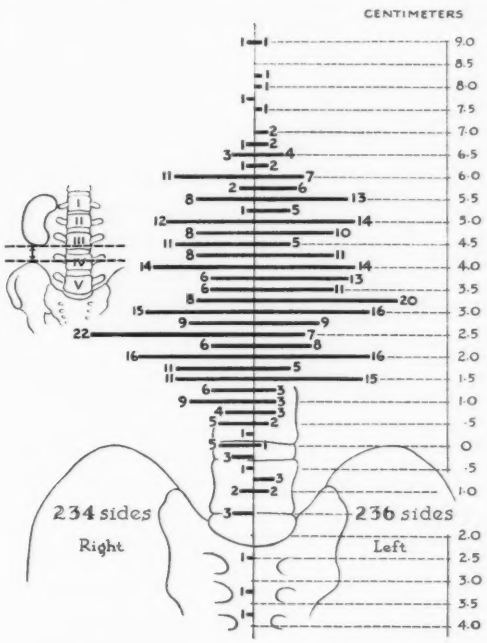


FIG. 3. Frequency record of the relationship of the inferior renal extremity to the iliac crest. Approximate range is +9 to −4 centimeters.

number and type of tributaries received, and the consequent degree of complexity of the venous tree.

In 30 specimens, the length of the venous portion of the renal vascular pedicle was measured (Fig. 9). In the present series, the length of the right renal vein varied from 20 to 45 millimeters, with an average length of 32 millimeters. Usually, there is a single right renal vein, but there may be doubling (Fig. 10d) or, in a rare instance, even trebling (Fig. 10a).

In contrast to the right side, the left renal vein ranged from 60 to 110 millimeters in length, with an average length of 84 millimeters, more than 2½ times that of the right renal vein (Fig. 9). The left renal vein, in its course from the hilus of the left kidney to the inferior vena cava, crosses and comes into intimate contact with a wide variety of visceral organs and parietal structures. The tributary pattern of the left renal vein is, consequently, far more complex than that of the right side.

Neither the renal arteries nor the renal veins are isolated from the vascular elements of the adjacent structures, either visceral or parietal. For example, the arterial supply of the kidneys is closely associated with the vessels for the suprarenal glands and the ovaries or testicles. When accessory renal arteries arise from the inferior phrenic arteries, or in association with the suprarenal arteries, they are likely to be small and numerous, and to penetrate the superior extremity of the kidney (Fig. 11a, right). On the other hand, accessory renal arterial branches from the internal spermatic or ovarian arteries are usually single, small, and may reach either the lower part of the renal hilus (Fig. 10c, bilateral) or the inferior extremity of the kidney (Fig. 11d, right). However, in general, renal arterial variations are of a relatively simple nature

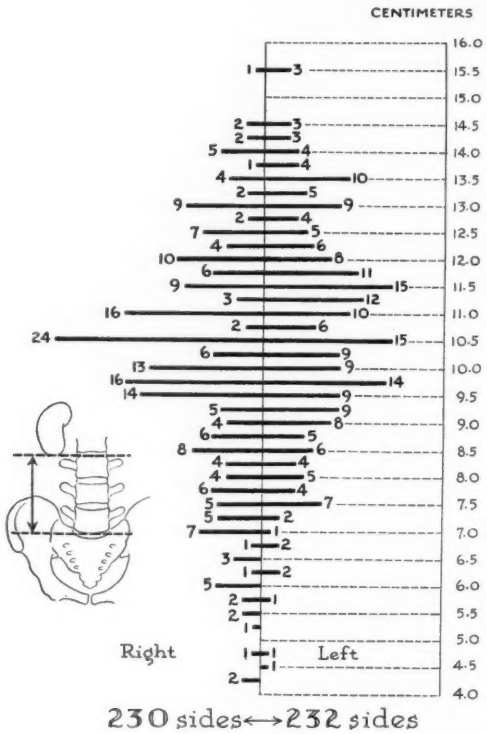


FIG. 4.

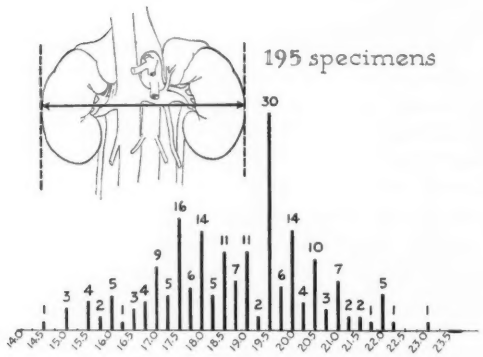


FIG. 5.

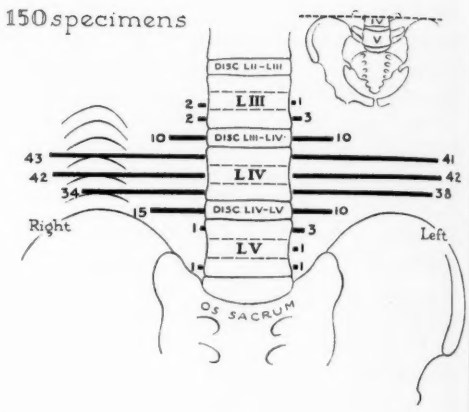


FIG. 6.

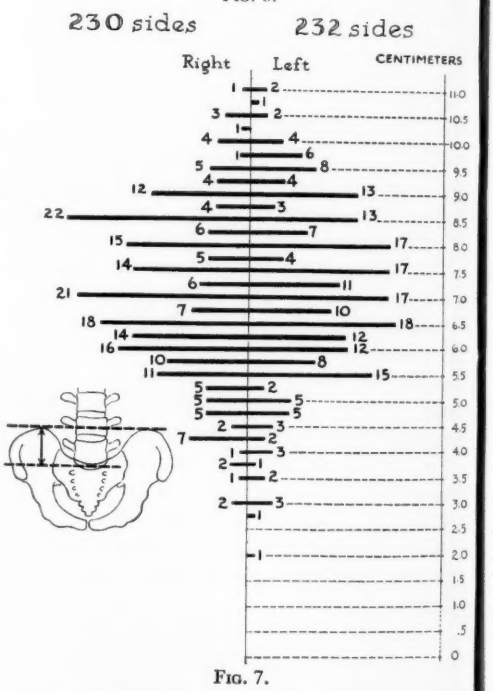


FIG. 7.

and consist of multiple vessels usually of aortic origin arranged in a stepladder-like pattern (Figs. 11a, bilateral; 11d, left; 10a, bilateral; and 10b). The chief exceptions occur in cases of pelvic and low midline, fused or unfused, kidneys. When multiple renal arteries occur on the right side, they may pass either dorsal or ventral to the inferior vena cava enroute to the kidney (Fig. 10a).

VISCERAL VENOUS CONNECTIONS

The left suprarenal vein is invariably a tributary of the left renal vein, either directly or by means of a common stem with the in-

FIG. 4. Frequency graph of distances between the levels of the inferior extremity of the kidney and the sacral promontory. Approximate range of variation is 4 to 15 centimeters.

FIG. 5. Frequency graph of distance between the lateral (convex) renal borders of the two kidneys. No examples of horseshoe kidneys were encountered in this series.

FIG. 6. Graphic record of the relation between vertebrae and iliac crests demonstrating inconstancy between skeletal landmarks.

FIG. 7. Record of the differences encountered in the skeletal framework: the distances from the sacral promontory to the iliac crests.

FIG. 8. Variations in interrelationship of the renal artery and the renal vein in 125 specimens. a, Artery dorsal to the vein on the right side in 58 bodies. b, Artery dorsal to the vein on the left side in 61 cases. c, Artery on the right side descends in a cephalic to caudal direction to a position ventral to the renal vein in 54 cadavers. d, Renal artery on the left side descends to a position ventral to vein in 51 specimens. e and f, Renal artery ascends in cephalic direction to assume a position ventral to the renal vein at the kidney hilus; 3 specimens on each side. g and h, Renal arteries situated cranial or caudal to their respective renal veins; 10 specimens on each side.

FIG. 9. Maximal, minimal, and average lengths of the renal pedicles in 30 successive specimens.

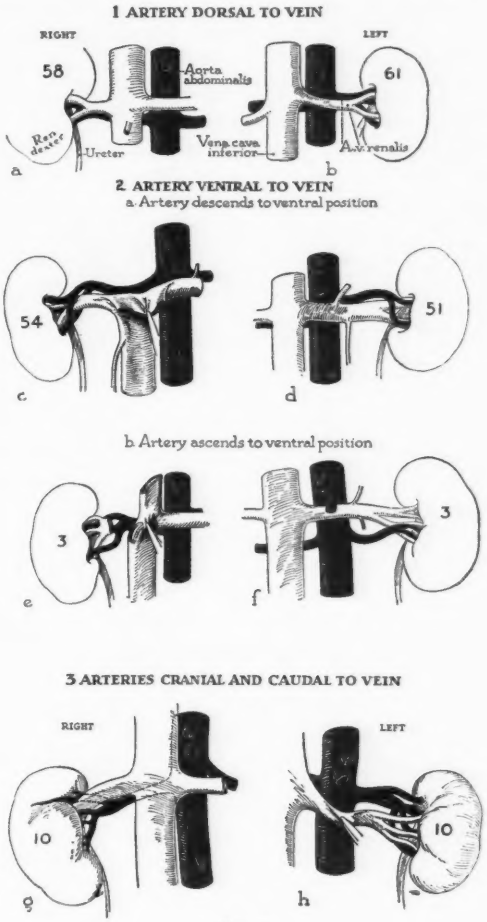


FIG. 8.

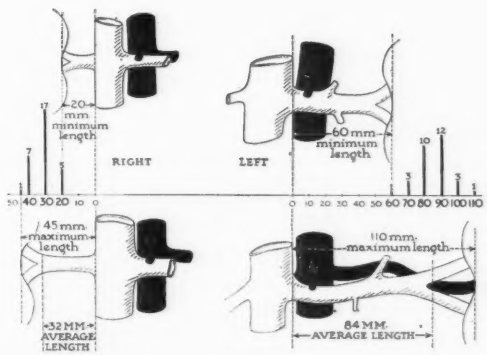


FIG. 9.

ferior phrenic. On the right side, the suprarenal vein almost always drains directly into the inferior vena cava. With rare exceptions, the left sex vein—internal spermatic or ovarian—joins the left renal vein, usually lateral to the entrance of the suprarenal and on the inferior surface. This type of termination occurs on the right side in only about one-fifth of the cases.

Other investigators have demonstrated additional visceral connections of the left renal vein. Cruveilhier demonstrated anatomic connections between the superior mesenteric and left renal veins; Duskes has shown minute communications between the left renal and pancreatic and splenic veins; Kolliker has described gross communications between the extrarenal and intrarenal veins which he termed "veini capsularis." Hollingshead and McFarlane, in an experimental study of renal venous obstruction in dogs, demonstrated the clinical importance of these capsular venous collateral channels. The capsular veins may empty into the internal spermatic or ovarian veins, the ureteric veins, the uterine veins, or into a patent segment of the obstructed renal vein. On

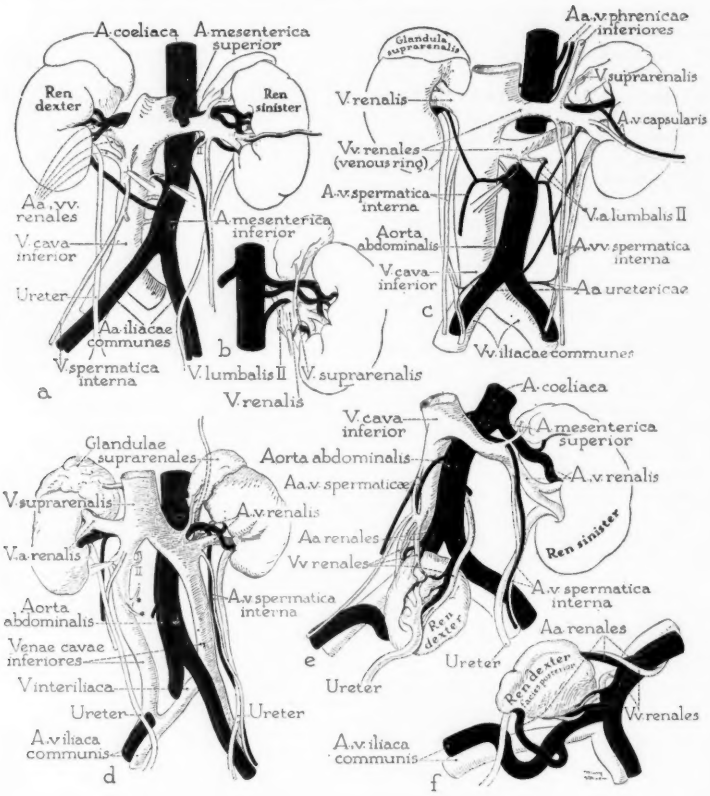


FIG. 10. Examples of variations in renal form, position, and blood supply. a, Renal pedicles rendered complex by the presence of supernumerary arteries and veins and by the occurrence of lumbar tributaries from retroaortic and deep paravertebral position. On the right side the upper or superior one of the pair of arteries reaches the renal sinus by passing dorsal to the inferior vena cava, while the other passes ventral to the caval vein. The postcaval vessel sends its branches downward to attain a position ventral to the largest of 3 renal veins; the precaval vessel, on the contrary, remains caudal or inferior to all of the other hilar elements. Small veins, of generally transverse course, enter the inferior vena cava from a retroaortic (prevertebral) position. On the left side the kidney is supplied by 3 renal arteries that arise from the aorta in an area just caudal to the origin of the superior mesenteric artery. The lowermost hooks around the second left lumbar vein, as the latter emerges from the substance of the psoas major muscle. In addition to the lumbar vein, and the usual suprarenal and spermatic tributaries, the renal vein receives, through one of its hilar vessels, a capsular vein which matches, in its course, a capsular artery. b, The vascular relationships of the left renal, lumbar, and suprarenal veins in the same specimen, shown by transecting the renal vein and turning it downward. c, Example of relative simplicity in constituency of the right renal pedicle in the presence of complexity in arrangement of structures on the left. On the right, the single large renal vein covers the main artery in an unusually short pedicle. An accessory renal artery is present; as a slender stem from a somewhat larger right internal spermatic artery, the supernumerary vessel ascends to the renal hilus. From the aorta, near its iliac bifurcation, a ureteric artery descends to the duct, to terminate where the ureter crosses the right common iliac artery. On the left side, the renal vein divides near the hilus of the kidney, the parts thus produced being limbs of a so-called circumaortic venous ring. The preaortic limb receives the inferior phrenic and suprarenal veins, through a common tributary, and 2 internal spermatic veins; the postaortic limb receives the second lumbar vein and a smaller vessel from the prevertebral or retroaortic connective tissue. As is regularly the case, the ventral limb courses transversely from the kidney to the inferior vena cava, whereas, the dorsal limb passes obliquely downward to reach a termination in the caval vein. A vein of capsular drainage, matching an artery derived from the renal, enters the ventral limb where the latter is formed by convergence of hilar tributaries. Two left ureteric arteries are present. Arising separately from the proximal segment of the left common iliac artery, these branches

Continued on facing page.

course in different directions; the cranial member ascends toward the renal pelvis, while the caudal member of the pair passes transversely toward the ureter, dividing in midcourse. The following vascular features also warrant notation: short, common trunk for the celiac and superior mesenteric arteries; doubling of the left inferior phrenic artery; presence of a small supernumerary renal artery on the left side, which, like that of the right, arose from the internal spermatic artery. d, Double inferior vena cava, together with contrasting constituency of the renal pedicles. The caval channels, both of great caliber, lie to the sides of the abdominal aorta; they communicate caudally through a channel which is situated dorsal to the right common iliac artery. The short suprarenal vein of the right side courses horizontally to the dorsum of the inferior vena cava, formed by the confluent channels; the suprarenal vein of the left side descends vertically to the upper segment of the left caval channel. On the right, a small accessory renal vein is a constituent of the pedicle; on the left, a supernumerary renal vein, dorsally placed, receives a communicating stem from the azygos system of the thorax. On the right, the renal artery reaches ventral position by ascending in front of a hilar vein; on the left side, a ventral position is attained by the artery's descent in front of the larger of the two renal veins. Both caval channels receive lumbar and prevertebral tributaries (on the right, numbered and indicated by asterisk, in relation to the retracted vessel). e and f, Kidneys, renal vessels, and related blood vessels in a case of pelvic kidney. f, The anomalous kidney has been rolled lateralward in order to demonstrate its relation to the common iliac artery and vein of the right side.

the basis of these experiments, the authors concluded that any vein in the immediate vicinity of the kidney, whether or not it normally has direct communications with the renal vein, may develop such connections upon occlusion of that vein.

PARIETAL VENOUS CONNECTIONS

Unlike the veins of the gastrointestinal tract, the left renal vein frequently receives tributaries from adjacent parietal areas. As already stated, the left inferior phrenic vein frequently drains into the left renal, through the suprarenal vein as an intermediary. Lumbar communications with the left renal vein occurred in more than half of the bodies studied. Most commonly, it is the second lumbar vein (Figs. 10a, b, c, and 11e), but frequently the third lumbar vein, and, on occasion, both the second and third lumbar veins (Fig. 11d) will communicate with the left renal vein. Such lumbar communications, although usually direct, sometimes combine with the genital vein before reaching the left renal vein (Fig. 11c). In a recent article, Davis, Milloy, and Anson described and figured examples of the lumbar venous plexus. Dissection of the psoas musculature is needed to expose the ladder-like patterns of the ascending lumbar veins and the paired segmental lumbar veins, together with their multiple anastomotic connections with the azygos, hemiazygos, common iliac, inferior vena cava, and left renal veins. Taken as a whole, they constitute an interconnecting system which extends from the sacral to the thoracic regions. Via these connections the left renal vein may be brought into direct venous contact with the vertebras, their discs and ligaments, the spinal cord, its meninges, and the lumbar and dorsal axial and appendicular musculature. The drainage pattern of the left renal vein is rendered more complex by the occurrence of left inferior vena cava (Fig. 10d), or a circumaortic venous ring (Fig. 10c). The dorsal limb of this ring quite frequently receives lumbar, azygos, and hemiazygos tributaries; less regularly, it receives branches from the retroperitoneal tissues and capsular branches from the perirenal fat and even from the renal parenchyma.

The variations in relationship of the renal arteries and veins were studied and recorded in 125 specimens (Fig. 8). In general, the following vascular relationships were encountered: In 47.6 per cent of the sides (58 right and 61 left), the renal artery or arteries were dorsal to the renal vein (Fig. 8a and b). In 42.0 per cent (54 right and 51 left), the renal artery descended from its more cranial aortic origin to a position ventral to the renal vein (Fig. 8c and d). In 2.4 per cent (3 right and 3 left), the renal artery ascended from a more caudal aortic origin to a position ventral to the renal vein (Fig. 8e and f). In 8.0 per cent of the sides (10 right and 10 left), the renal arteries and veins were not in a direct dorsal or ventral relationship. Instead, the renal arteries were definitely either cranial or caudal to the veins (Fig. 8g and h).

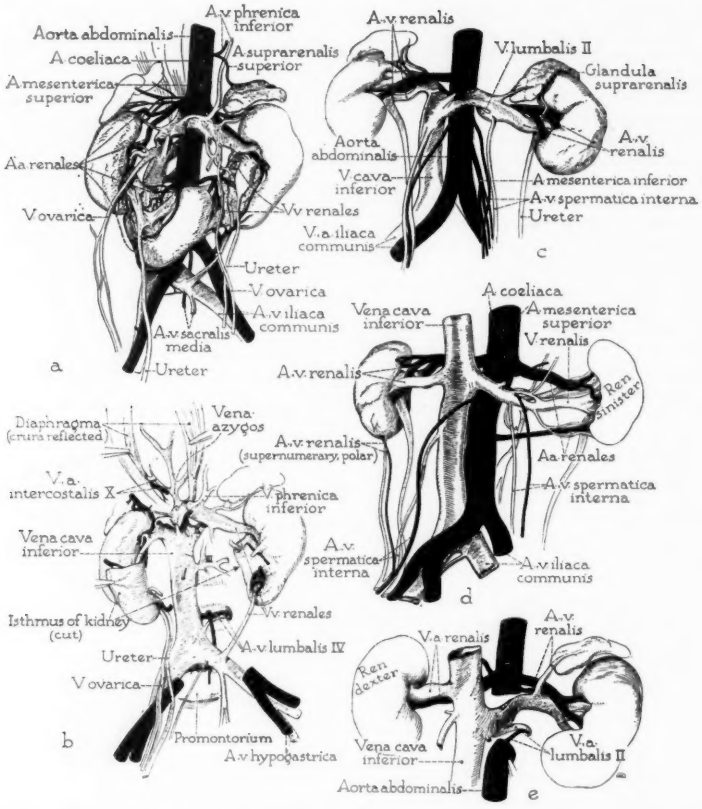


FIG. 11. Renal variations, continued. a, The kidneys are connected by a broad isthmus of irregular form—being considerably lower on the right side than on the left. On the right side the ureter is formed by the junction of two main, widely divergent portions, which were joined below by a third portion. On the left, two portions are evident; however, their junction is quickly established—so that the ureter does not seem to be of Y-shaped form. On the right side, there are two renal arteries. The upper or superior one arises from the aorta approximately 1 centimeter below the point of origin of the superior mesenteric. In its descent toward the sinus of the kidney, the artery gives off a branch to the suprarenal gland and one to the superior extremity (upper pole) of the kidney. Skirting the superomedial border of the isthmus, the artery anastomoses with the second vessel of supply to the right side. The lower (caudal) member of the pair arises by a common stem with a vessel of the opposite side. In addition to the suprarenal arteries mentioned above as being renal in origin, a small suprarenal vessel arises from the aorta itself near the origin of the upper renal. On the right side, the inferior extremity (lower pole) of the kidney receives two arteries from the common iliac. The renal vein of the right side receives the ovarian vein. b, Details of deep renal anatomy in the same specimen, revealed by transecting the isthmus and excising the aorta, its divisions and chief branches. On the right side, the ovarian vein is a tributary of the renal vein. In the midline and to the left, the azygos vein descends between the crura of the diaphragm to communicate with the inferior vena cava and the second left lumbar vein. A large left renal vein terminates in the inferior vena cava; a smaller descends to the left common iliac vein. The left renal vein receives the customary tributaries—inferior phrenic, suprarenal, ovarian. c, On the right side, a single renal artery descends in front of the vein, the crossing occurring midlength of the pedicle. When the sinus is reached, the artery is the lowermost element. Two small suprarenal arteries arise from the renal; a suprarenal vein empties into the renal. The internal spermatic artery arises from the aorta at renal level; the corresponding vein empties into the inferior vena cava at the lower border of the pedicle.

On the left side, matching, in general, the interrelationships of artery and vein already described, the renal artery of the left side descends to cover the vein—as the kidney is approached—by dividing into three hilar portions. The renal vein receives the following vessels as tributaries: two suprarenal vessels, one near the caval termination and the other near the kidney; internal

Continued on facing page.

spermatic vein. The internal spermatic artery arises from the aorta 2 centimeters below the lower border of the pedicle. In summary, the chief features are: exchange of position of the main vessels of the renal pedicles—the artery on each side passing to ventral position by descending from a more cranial position (at the point of aortic origin); occurrence of a large lumbar tributary on the left side. Other features of interest are: termination of a right suprarenal vein in the renal (not, as commonly found, in the inferior vena cava); apparent doubling of the left suprarenal vein (with considerable interdistance between points of ending in the renal). d, On the right side there is an elongated pattern at the renal sinus, the renal artery sending a descending branch to the inferior aspect of the sinus (of an unusually small kidney). The internal spermatic vein receives, at the level of the sacral promontory, a vein from the inferior extremity (lower pole) of the kidney. A corresponding artery probably arose from the internal spermatic. On the left side, two renal arteries are present: the upper one arises from the aorta just caudal to the level of the superior mesenteric, the lower near level of origin of the inferior mesenteric. The arteries are 6 centimeters apart at the aortic ends, 2.5 centimeters apart where they enter the sinus. The internal spermatic artery, coursing transversely or horizontally beneath the renal vein, passes through a hiatus in the latter, about midway between the inferior vena cava and the kidney, then descends vertically to the pelvis. The left renal vein receives the following tributaries from medial to lateral: suprarenal and second lumbar (above); internal spermatic and third lumbar (below); polar tributary (below), which is a conjoined vessel, formed by union of small veins near the lower one of the pair of renal arteries. Both common iliac arteries follow a sigmoid course. e, On the right side, the renal pedicle of the expected type, that is, one in which the vein lies ventral or anterior to the artery. However, on the left half, two noteworthy features occur: hilar divisions of the renal artery descending to a position ventral to the corresponding veins, and termination of the second left lumbar vein in the renal.

SURGICAL SIGNIFICANCE

Variations in the positional anatomy of the kidney and its vascular supply are of clinical importance to the general and vascular surgeon, and to those who specialize in either urology or gynecology.

Visualization of the kidney and its collecting system by means of intravenous and retrograde pyelography has been supplemented by the development of the technique of translumbar aortic puncture with the injection of solutions of radio-opaque substances. Smith and Harvard believe that in surgical procedures which involve renal ectopia and in all cases of congenital renal anomalies which require surgery preoperative studies of the renal arterial supply are always helpful, and at times essential.

Impairment of the renal arterial supply or partial obstruction of the renal venous outflow, caused either by disease processes or by surgical manipulation, may result in the production of pressure substances by the involved kidney and subsequent development of systemic hypertension. Therefore, in plastic procedures involving the renal pelvis or ureter, or even in procedures involving simple ligation and severance of an accessory renal artery or vein, familiarity with the common types of vascular supply is mandatory.

Use of the left renal vein for the decompression of portal hypertension by means of a splenorenal venous shunt has greatly increased the surgical importance of this rather complex venous tributary. In those cases in which the left renal vein is a simple channel that continues undivided to the inferior vena cava, mobilization and utilization of the vessel would be a relatively simple surgical procedure (Fig. 11c). However, surgical difficulty would be presented, in attempting splenorenal anastomoses, by specimens of more complex venous pattern (Figs. 10c and d and 11d and e).

A pelvic kidney (Fig. 10e and f), if urinary drainage be adequate, gives no distressing symptoms. But its presence in pregnancy would indicate delivery by cesarean section because, by location, the pelvic kidney would block passage of the fetal head. Hydronephrosis, infection, and calculus formation in an unrotated, ectopic kidney of this type would be the result of impaired urinary drainage.

Ockerblad states that, on occasion, aberrant renal arteries may in themselves be responsible for pain (compare Figs. 11a and d and 10a, b, c, d, e, and f). He believes that the cause is tension upon the aberrant vessels, and has advocated their ligation and severance. In the discussion of such surgery, Gibson warns against the sacrifice of anomalous vessels, arteries in particular. He points out that because the arteries are

terminal—that is, without anastomoses—ligation might result in an anemic infarct, with resultant jeopardy to renal integrity, possible necrosis, infection, and even systemic hypertension. Small arteries may be sacrificed with impunity, but if medium or large, the artery should first be compressed to determine the amount of renal tissue that becomes blanched before deciding to obliterate the vessel.

The occurrence of an ectopic kidney, with its complex vascular pedicle, creates a difficult problem in vascular surgery (compare Fig. 10e and f). The lodgement of an embolus above or in the S-shaped segment of the right common iliac artery or severe arteriosclerotic narrowing of the lumen of this vessel would most probably necessitate a right nephrectomy prior to definitive surgical correction of the vascular condition. Knowledge of this ectopic organ and its vascular pedicle, supplemented by information on the function of the left kidney prior to operation would, undoubtedly, prove most helpful. Specimens of this type serve to illustrate the direct relationship between the position of the kidney and the levels of origin of the vascular constituents of the renal pedicle.

Approximately one-fourth of all patients with horseshoe kidneys (Fig. 11a and b) require operation, usually because of calculus formation and hydronephrosis. Culp and Winterringer have reviewed the surgical procedures utilized on 106 patients with true horseshoe kidneys, treated at the Mayo Clinic. They found that nephrectomy with removal of half of a horseshoe kidney was the operation most frequently used.

This operation is fraught with complications, of which postoperative hemorrhage and fistula formation were the most significant. The authors stressed the importance of studies designed to determine the nature and extent of the renal isthmus, which may vary from a fibrous band (Fig. 11b) to a broad zone of functioning renal cortex. Careful identification of all anomalous vessels and determination of their areas of renal supply prior to ligation and severance seem most essential. Removal of one-half of a horseshoe kidney should include excision of all cortical tissue up to the adjacent pole of the remaining kidney, rather than simple division of the isthmus at a convenient level. Culp and Winterringer have pointed out that, occasionally, the isthmus may have a separate blood supply that can be ligated and controlled; however, in other cases, the entire blood supply to both segments of the horseshoe kidney enters through the isthmus, in which instance ligation of the vascular pedicle would prove disastrous.

Their results in the treatment of calculi and hydronephrosis in horseshoe kidneys by more conservative means, pyeloplasty—usually of the Foley Y-type—with symphysiotomy and nephropexy, are encouraging.

Recently, Nathan described the occurrence in 3.5 per cent of his cases of a supernumerary artery to the lower extremity of the kidney derived from the aorta below the level of the corresponding renal vein. The aberrant vessel first ascended dorsal to the renal vein; then, after arching over the latter, it descended to enter the renal parenchyma (Fig. 10a). In these cases the renal vein appeared constricted and angulated beneath the arch of the anomalous artery.

Notkovich (15, 16) described compression of the renal vein by gonadal arteries (his type III) which, after arising either from the aorta or from the renal artery, dorsal and caudal to the renal vein, then followed a recurrent course cranialward, to loop over the renal vein. On the left side, in as many as 33.8 per cent of cases, the renal vein is crossed by a gonadal artery (compare Figs. 10e and 11d); whereas, on the right side this relationship occurs in but 16.3 per cent of cases. Resultant compression is manifest through angulation and narrowing of the renal veins at the sites of crossing of the gonadal arteries. Cotrim and De Barros Barboza have demonstrated roentgenologically, in a case of varicocele, in the erect position, that the blood flow in the testicular vein is inverted by the effect of compression

of the renal vein. A venous shunt is established whereby blood passes from the renal to the iliac vein through anastomoses with the deferential, funicular, and external pudendal veins.

CONCLUSIONS

The topographic anatomy of the two kidneys and their relationships to adjacent structures, both visceral and parietal, is subject to considerable variation. Directly related to this variation in renal position are the variations which occur in the levels of origin of the arteries of supply and levels of termination of the renal veins. Generally speaking, a "thoracic" kidney will almost invariably have a vascular pedicle that arises at a cranial level, whereas, a pelvic kidney will regularly have communications with the lower abdominal and pelvic vessels.

Conformity to the pattern of the simple pedicle, depicted in some texts of anatomy and surgery, is encountered in approximately one-quarter of the cases studied, and this more frequently on the right than on the left side.

The relative simplicity of the right renal pedicle is due primarily to the shortness of the vein which receives an ovarian or internal spermatic tributary infrequently and other tributaries rarely. In contrast, the left renal vein, whose length may be five times that of the right renal vein, has a tributary pattern which is considerably more complex. The suprarenal and the inferior phrenic veins are constant tributaries. Additionally, the internal spermatic, or ovarian, and the second lumbar veins regularly end in the renal.

Persistence of portions or of all of the left caval vein of the fetal circulatory system renders even more complex the parietal tributary patterns of the left renal vein. Surgical difficulties and hazards are created by the occurrence of these complicated venous patterns in the performance of nephrectomy, and especially in splenorenal shunt for portal hypertension. These difficulties are matched by those presented in the surgery of lumbar, pelvic, and horseshoe kidney, again because of the complexity of their vascular pedicles.

REFERENCES

1. Anson, B. J., Cauldwell, E. W., Pick, J. W., and Beaton, L. E. The blood supply of the kidney, suprarenal gland, and associated structures. Surg. Gyn. Obst., 1947, 84: 313–320.
2. Idem. The anatomy of the perirenal system of veins with comments on the renal arteries. J. Urol., Balt., 1948, 60: 714–737.
3. Anson, B. J., and Kurth, L. E. Common variations in the renal blood supply. Surg. Gyn. Obst., 1955, 100: 156–162.
4. Cotrim, Souza E., and De Barros Barboza, Varbas. Estudio radiologico in vivo de circulacion de varicocele por medio de liquidos de contraste. Rev. paul. med., 1941, 19: 341–351.
5. Cruveilhier, J. Anatomie Descriptive. Vol. III. Paris: Bechet Jeune, 1834.
6. Culp, O. S., and Winterringer, J. R. Surgical treatment of horseshoe kidney; comparison of results after various types of operations. J. Urol., Balt., 1955, 73: 747–756.
7. Davis, R. A., Milloy, F. J., and Anson, B. J. Lumbar, renal, and associated parietal and visceral veins based upon a study of 100 specimens. Surg. Gyn. Obst., 1958, 107: 1–22.
8. Duskes, E. Extrarenal venous circulation in cases of congenital polycystic kidneys; unusual varicocele communicating between splenic and renal veins. Arch. Surg., 1927, 15: 580–588.
9. Gibson, T. E. Discussion of article by Ockerblad (17). J. Urol., Balt., 1952, 67: 810–814.
10. Harvard, M. Renal angiography. J. Urol., Balt., 1953, 70: 15–19.
11. Hollingshead, W. H., and McFarlane, J. A. The collateral venous drainage from the kidney following occlusion of the renal vein in the dog. Surg. Gyn. Obst., 1953, 97: 213–219.
12. Kolliker, A. Handbuch der Gewebelehre des Menschen. Leipzig: W. Engelmann, 1867.
13. McClellan, R. E. A low lying left kidney. J. Urol., Balt., 1956, 75: 198–199.
14. Nathan, H. Observations on aberrant renal arteries curving around and compressing the renal vein. Circulation, 1958, 18: 1131–1134.
15. Notkovich, H. Testicular artery arching over renal vein; clinical and pathological considerations with special reference to varicocele. Brit. J. Urol., 1955, 27: 267–271.
16. Idem. Variations of the testicular and ovarian arteries in relation to the renal pedicle. Surg. Gyn. Obst., 1956, 103: 487–495.
17. Ockerblad, N. F. Aberrant renal arteries which in themselves produce pain. J. Urol., Balt., 1952, 67: 810–814.
18. Pick, J. W., and Anson, B. J. Renal vascular pedicle; anatomical study of 430 body-halves. J. Urol., Balt., 1940, 44: 411–434.
19. Robbins, J. T., and Lich, R., Jr. Thoracic kidney. J. Urol., Balt., 1954, 72: 133–134.
20. Seib, G. A. Azygos system of veins in American whites and American Negroes, including observations of the inferior caval venous system. Am. J. Phys. Anthrop., 1934, 19: 39–163.
21. Smith, P. G. A résumé of the experiences in the making of 1500 renal angiograms. J. Urol., Balt., 1953, 70: 328–331.
22. Spillane, R. J., and Prather, G. E. High renal ectopy. J. Urol., Balt., 1959, 62: 441–445.

SERUM LIPID PATTERNS BEFORE AND AFTER CASTRATION OF THE HUMAN FEMALE

RICHARD W. STANDER, M.D., and JOHN N. LEIN, M.D., Indianapolis, Indiana

ALTHOUGH THE EXACT RELATIONSHIP of serum lipids to the development of atherosclerosis in the human is unknown, clinical observations and experimental work of the past few years have suggested not only an association between abnormal serum lipid patterns and the development of atherosclerosis but also that certain of the sex steroids may act in an inhibitory manner with respect to the development of cardiovascular disease.

Pick and his associates found a high incidence of coronary atherosclerosis in cockerels on a high cholesterol diet in which elevated values for total serum cholesterol and high ratios of total cholesterol to phospholipid were present. A group of cockerels fed a similar diet but in which total cholesterol and cholesterol to phospholipid ratio values were lowered by administration of estradiol benzoate showed atherosclerosis to a lesser degree.

The relative rarity of coronary artery disease in women under the age of 40 and the common clinical observation that the incidence of proved myocardial infarction rises rapidly in women after the menopause have suggested a relationship between ovarian function and the inhibition of coronary atherosclerosis in women. The cause of such a relationship has been furthered by the autopsy findings of Wuest and coworkers, who reported a higher incidence of coronary atherosclerosis in women who had undergone previous surgical castration than in women of the same age group with intact ovaries, although their findings are not corroborated in a recent article by Novak and Williams.

From the Department of Obstetrics and Gynecology, Indiana University Medical Center, Indianapolis, and the Marion County General Hospital, Marion, Indiana.

Additional evidence has been supplied by Oliver and Boyd (5) that partition of the serum lipids is directly or indirectly influenced by ovarian estrogen secretion, the total serum cholesterol and the ratio of cholesterol to phospholipid tending to be highest at those points in the menstrual cycle at which estrogen excretion is lowest. They have also supplied evidence that not only do surgical castrates have higher levels of total serum cholesterol and higher ratios of total cholesterol to phospholipid than noncastrates of the same age, but also that the former have a higher incidence of clinically detectable heart disease than the latter (7). Additional evidence that sex steroids play a role in the pattern of serum lipids is supplied by reports dealing with the effect of exogenous estrogen in reduction of total serum cholesterol and ratio of cholesterol to phospholipid, hereafter referred to as C/P ratio, in both males and females (6).

Thus, by retrospection and analogy, evidence has accumulated to indicate that ovarian secretion may provide protection against coronary artery disease and that ablation of the ovaries may create changes in the serum lipid pattern which may be associated with coronary atherosclerosis. This study was initiated to compare the serum lipid patterns in the female before and after castration.

MATERIAL AND METHODS

Total serum cholesterol was determined by the method of Zlatkis and associates, and serum lipid phosphorus values were obtained by the technique outlined by the United States Naval Medical School. The latter values were then converted to phospholipid by multiplication by 25.

TABLE I.—COMPARATIVE DATA ON TOTAL SERUM CHOLESTEROL AND PHOSPHOLIPID IN HEALTHY FEMALES OF REPRODUCTIVE AGE AND IN GYNECOLOGIC PATIENTS BEFORE AND AFTER CASTRATION

Variable		*24 untreated patients*	*28 treated patients*		
			Before treatment	*After treatment*	*Amount of change*
Total cholesterol, mgm. per cent	Mean	187.42	183.85	195.11	+11.26
	S.D.	38.77	68.50	45.68	
Phospholipid, mgm. per cent	Mean	241.12	240.89	272.93	+32.04
	S.D.	42.10	58.50	52.50	
Ratio of total cholesterol to phospholipid	Mean	0.789	0.758	0.733	+0.025
	S.D.	0.169	0.154	0.175	

Two groups of patients were studied. The first consisted of 24 healthy women of reproductive age with normal, regular menses. Since serum lipids are known to fluctuate throughout the menstrual cycle, single determinations of total serum cholesterol and phospholipid were procured without regard to placement of the sampling with respect to timing within the individual's menstrual cycle in order to obtain an average lipid distribution in the 24 patients of this age group. Patients of both clinic and private category were utilized. Seventeen of the patients were colored and the remaining 7 were white.

The second group consisted of 28 gynecologic patients who were ultimately castrated for a variety of disorders. Pretreatment and posttreatment determinations of total cholesterol and phospholipid were carried out. Although it is possible that some of these patients may have had precastration disturbances of ovarian function by virtue of the disorders prompting gynecologic treatment, a requisite for inclusion in the study was that regular menstruation had occurred until the time of therapy. Again, pretreatment sampling was carried out without regard to placement in the menstrual cycle in order to obtain average lipid values for this group. There were 12 colored and 16 white patients among those in the treated group.

Surgical castration was carried out in 23 patients of the treated group. Major pathologic diagnoses in these patients were chronic pelvic inflammatory disease in 8, uterine leiomyomas in 6, endometriosis in 3, intraepithelial carcinoma of the cervix in 3, uterine leiomyosarcoma in 1, benign cystic ovarian teratoma in 1, and the remaining patient in the surgically castrated group underwent a Wertheim hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix, stage 1.

Five patients in the treated group were castrated by combined external irradiation and radium applications of the Manchester type for carcinoma of the cervix, stages 1 and 2. These patients received an estimated dose of 4,500 roentgens to each ovary. A total of 625 roentgens to each ovary has been demonstrated to be sufficient for castration of the adult human female. For purposes of follow-up, the last day of radiation therapy was arbitrarily chosen as the point of castration. None of the 5 patients menstruated after irradiation.

Patients in neither group had received hormone therapy prior to initial lipid determinations, and patients in the treated group received no hormones during the posttreatment observation period. Dietary factors were not assessed in either group, and no dietary control was imposed on the treated patients during the period of follow-up.

RESULTS

Initial analysis of the data included comparison of the ages of the untreated group with the ages of those ultimately castrated. The 24 patients of the untreated group ranged from 18 to 40 years, the mean age of the group being 26.88 years. Ages in the treated group at the time of pretreatment lipid determinations ranged from 21 to 49 years with a mean age of 37.43 years. The

treated group members were found to be significantly older than those in the untreated group with $p<.001$.

Mean values for total serum cholesterol, phospholipid, and C/P ratio for the untreated group are shown in Table I, as are mean values for these modalities prior to treatment in the 28 patients with gynecologic disorders. The p values for the differences in the means of total serum cholesterol, phospholipid, and C/P ratio between the untreated patients and the gynecologic patients prior to treatment are $<.90$, 1.00, and .30, respectively. Although positive homogeneity is not established by lack of a statistically significant difference between characters of two groups, the results suggest that, within the limitations of the modalities tested, a gynecologic patient in her late reproductive years enjoys the same homeostasis of serum lipids as her younger, healthier sister.

Serum lipid values in the treated group after castration were then compared to pretreatment levels to determine the effects of the gynecologic procedures. Eighty-four posttreatment lipid determinations were carried out in the 28 castrated patients at intervals varying from 1 to 14 months after castration by surgical means or by irradiation. The number of determinations varied from 1 to 6 per individual; thus, considerably more data were available for some patients than for others. The index of change of serum lipids after castration was determined for each individual by comparing her pretreatment values to the mean of her postcastration determinations.

With respect to total cholesterol, 18 patients showed an increase and 10 showed a decline after ablation of the ovaries. Nineteen patients had a rise in phospholipid after castration, whereas 9 patients showed decreases in these values. The ratio of total cholesterol to phospholipid increased in 11, decreased in 15, and remained unchanged in 2 patients.

The mean values for cholesterol, phospholipid, and C/P ratio after castration are shown in Table I, and the degrees of change from pretreatment values are listed. Because of the wide fluctuations of the individual means of the posttreatment lipid values above and below pretreatment values, examination of the raw data failed to lend statistical significance to the upward trend of total serum cholesterol and phospholipid after castration. Similarly, the slight reduction in C/P ratio failed to achieve statistical significance. However, when the distributions of changes that followed castration were converted to normalized T-score distributions and tested for significant deviations between the means of these distributions and the value corresponding with no change, the upward trends noted in total serum cholesterol and phospholipid after castration were found to have p values of $<.05$ and $<.02$ and are considered significant. The decline in C/P ratio of $p<.40$ which was noted after castration was not reliable.

DISCUSSION

The marked variation in behavior of total serum cholesterol and phospholipid among patients after castration suggests that factors other than the presence of ovarian tissue influence the partition of serum lipids. Possibly diet and hereditary factors are also determinants in this respect. Yet the over-all influence of the removal of ovarian tissue is indicated by the biochemical behavior of the group as an entity with significant elevations of total cholesterol and phospholipid occurring within a 14 month period after castration. Whether or not such changes in themselves may be important with respect to the ultimate development of cardiovascular disease is not known. Another unknown quantity is the end point of the change in the pattern of serum lipids that follows castration. Possibly a longer period of observation would indicate further change in the values for total serum cholesterol and phospholipid from pretreatment levels, as well as a significant change in C/P ratio.

Preservation of ovarian function in relatively young women undergoing hysterectomy for a benign disorder is a tenet advocated by the majority of gynecologists for many years. This concept antedated present research concerning the possible ovarian influence in protection against cardiovascular disease and was based upon the desire to prevent vasomotor instability, atrophy of estrogen-dependent structures and infrequent emotional reactions to removal of gonadal tissue. Although occasional cystic and degenerative changes do occur in seemingly normal ovaries after total hysterectomy, few gynecologists would agree with Grogan and Duncan that their incidence is sufficiently high to warrant the prophylactic removal of normal ovarian tissue at the time of hysterectomy in any patient regardless of her age.

There is considerably more divergence of opinion regarding preservation of ostensibly normal ovaries when hysterectomy is performed on the patient nearing the menopause. In the patient over 40, normal ovaries are frequently removed as prophylaxis against ovarian cancer and upon the assumption that their role in the individual's biologic economy will be short-lived. The data obtained in this study suggest that ovarian function in relationship to certain metabolic phenomena is just as important to the patient of 40 as it is to the 25 year old. In view of this and other recent studies cited, the surgeon's attitude toward sacrifice of normal ovarian tissue should be reexamined.

The probability of ovarian carcinoma developing in any woman who has reached the age of 45 is less than 0.9 per cent, with a constant decline from that age on. This is the incidence reported by Randall and associates and is derived from areas in which cancer is a reportable disease. Hollenbeck has already cited the case for preservation of normal ovaries regardless of the patient's age at the time of hysterectomy, believing that the large number of women cast into the menopause is not justified for prevention of the rare case of ovarian cancer. It might also be pointed out that the majority of those who practice prophylactic oophorectomy in conjunction with abdominal hysterectomy do not share the same enthusiasm for removal of ovaries at the time of vaginal hysterectomy, a paradox probably precipitated by the greater surgical effort required in the latter cases.

In addition, events of the past decade have cast serious doubt on the concept that all ovarian function terminates with cessation of the menses. Many women show significant estrogen effect in the vaginal mucosa for years after the cessation of menstruation. Randall and his co-workers believed that the incidence of hypertension was higher in those postmenopausal women who had estrogen-deficient vaginal smears than in those whose smears indicated a higher order of estrogen activity. Exactly what portion of the estrogenic effect may be the result of ovarian activity is difficult to assess, for Struthers, working with vaginal smears, and Bulbrook and Greenwood, measuring urinary estrogen, have indicated that sources other than the ovary may be responsible for a portion of postmenopausal estrogenic activity. Yet postmenopausal ovarian activity is strongly suggested by the report of Sherman dealing with the interrelationship of pituitary, ovary, and endometrium in endometrial carcinoma.

Further research will undoubtedly clarify the role of ovarian function in the homeostasis of serum lipids and the relationship of the latter to coronary artery disease. In the meantime, one must consider that gonadal tissue in the gynecologic patient in her forties may still play a vital role in metabolism, even though its reproductive capacity is diminished. In such patients, oophorectomy may be indicated by virtue of the primary disorder for which hysterectomy is being performed or ovarian abnormalities noted at the time that laparotomy is performed, but the normal gonad should not be eliminated by the same surgical reflex as is the appendix.

REFERENCES

1. Bulbrook, R. D., and Greenwood, F. C. Persistence of urinary oestrogen excretion after oophorectomy and adrenalectomy. Brit. M. J., 1957, 1: 662.
2. Grogan, R. H., and Duncan, C. J. Ovarian salvage in routine abdominal hysterectomy. Am. J. Obst. Gyn., 1955, 70: 1277.
3. Hollenbeck, Z. J. R. Ovarian cancer-prophylactic oophorectomy. Ann. Surg., 1955, 21: 442.
4. Novak, E. R., and Williams, T. J. Autopsy comparison of cardiovascular changes in the castrate and normal woman. Am. J. Obst. Gyn., in press.
5. Oliver, M. F., and Boyd, G. S. Changes in the plasma lipids during the menstrual cycle. Clin. Sc., Lond., 1953, 12: 217.
6. Idem. The influence of the sex hormones on the circulatory lipids and lipoproteins in coronary sclerosis. Circulation, 1956, 13: 82.
7. Idem. Effect of bilateral ovariectomy on coronary-artery disease and serum lipid levels. Lancet, Lond., 1959, 2: 690.
8. Pick, R., Stamler, J., Rodbard, S., and Katz, L. N. The inhibition of coronary atherosclerosis by estrogens in cholesterol-fed chicks. Circulation, 1952, 6: 276.
9. Randall, C. L., Birtch, P. K., and Harkins, J. L. Ovarian function after the menopause. Am. J. Obst. Gyn., 1957, 74: 719.
10. Sherman, A. J., and Woolf, R. B. An endocrine basis for endometrial carcinoma. Am. J. Obst. Gyn., 1959, 77: 233.
11. Struthers, R. A. Post-menopausal estrogen production. Brit. M. J., 1956, 1: 1331.
12. United States Naval Medical School. Clinical laboratory procedures. P. 228. Bureau of Naval Personnel, Navpers 108685, A 111.
13. Wuest, J. H., Dry, T. J., and Edwards, J. E. The degree of coronary atherosclerosis present in bilateral oophorectomized women. Circulation, 1953, 7: 801.
14. Zlatkis, A., Zak, B., and Boyle, A. J. Report on a new method for the direct determination of serum cholesterol. J. Laborat. Clin. M., 1953, 41: 486.

OBSERVATIONS CONCERNING SPLEEN HOMOTRANSPLANTATION IN NORMAL AND IRRADIATED ANIMALS

BERNARD FISHER, M.D., F.A.C.S., SIL H. LEE, M.D., and
EDWIN R. FISHER, M.D., Pittsburgh, Pennsylvania

THE FEW REPORTS of autotransplantation, homotransplantation, and heterotransplantation of the entire spleen which have appeared in the literature since 1900 have primarily concerned themselves with technical accomplishment. No documentation of the histologic fate of such transplants similar to that to be found for homotransplanted kidneys is available. Such information was obtained during the course of investigation of the following two problems related to spleen homotransplantation.

Jacobson and associates (10, 11, 12) demonstrated that shielding of the spleen and the implantation of normal mouse spleen into the peritoneal cavity of irradiated mice after exposure had a protective effect against radiation lethality. These findings led to the concept that normal spleen elaborated a humoral radiation recovery factor. Subsequent reports by others tended to substantiate this hypothesis. Cole and co-workers (3, 4) found that the protective effect which they had previously obtained with the intraperitoneal injection of buffered homogenates of normal spleen was due to the nuclear fraction of the cells. Ellinger and Savitsky subsequently reported that cell-free extracts prepared from normal spleens have lowered the mortality from irradiation. To lend further support to the possibility that a splenic humoral factor is concerned, Allen and associates reported that freshly drawn cell-free plasma obtained from the splenic veins of normal animals afforded postirradiation protection to rabbits. The evidence for this theory has been critically reviewed by Loutit, Brown and associates, and Kaplan. Data have been presented, however, which favor the hypothesis that the irradiation protection is a function of "cellular repopulation" and/or "transitory activity" of injected cells pending recovery of recipient marrow, rather than a humoral factor. Because of this apparent controversy, it seemed worth while to homotransplant the intact spleen into animals which had received total body irradiation of such magnitude that the rejection response of the host to the transplant was suppressed and the survival rate of irradiated animals minimal.

The second investigation which concerned us was the result of a prior study of canine renal homotransplants in various stages of rejection using the fluorescent antibody technique of Coons and Kaplan. Since we had reported (8) no preferential localization of globulin in the rejected kidneys and had failed to disclose antibodies in the recipient's serum which demonstrated an affinity for kidney structure, it was deemed worth while to repeat these studies on the homotransplanted spleen.

We therefore present our experiences with spleen homotransplantation with special reference to: (a) the histologic picture which occurs during various stages of rejection; (b) the protective effect of such transplants after lethal doses of irradiation; (c) the use of the fluorescent antibody technique as a means of gaining information concerning the rejection phenomenon.

From the Department of Surgery, Laboratory of Surgical Research, and Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh.
Supported by U. S. Public Health Service Grant No. C-3731 and Health, Research and Services Foundation Grant No. B-11.

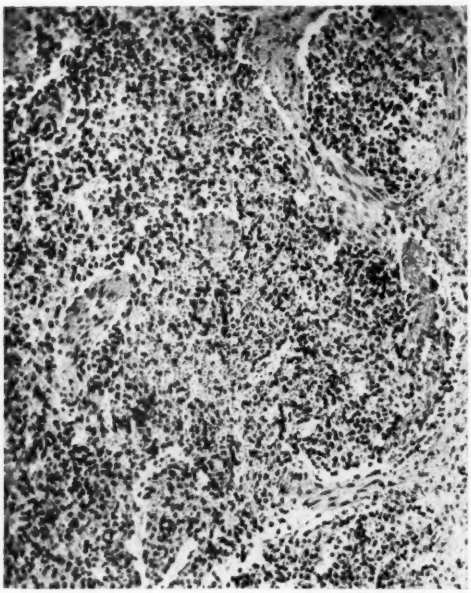


FIG 1. Photomicrographic appearance of spleen 3 days after transplantation. Fibrin mass is noted in subcapsular sinusoid. ×100.

METHODS

One hundred and four male and female mongrel dogs weighing 10 to 15 kilograms, were used for this study. All dogs had been immunized against distemper and were part of the colony for more than 6 weeks. They were fed ad libitum purina dog chow supplemented with milk, karo syrup, and water.

All spleen homotransplants were performed by one of us using meticulously sterile technique. In each instance, the donor dog was prepared by freeing its splenic artery from numerous small tributaries as far as the celiac axis. The hepatic and left gastric arteries were ligated and divided so that a 1 inch segment of aorta with attached celiac and splenic artery could be resected. The splenic vein was similarly freed to its junction with the portal vein and was transected with an attached cuff of the latter vessel. After mobilization of the spleen with its vascular attachments and before removal, heparin solution—5 milligrams per kilogram—was injected into the aorta of the donor animal. Each recipient animal was prepared by mobilization of its aorta above the trifurcation, and the vena cava was similarly freed so that an elliptic section of its wall could be removed to accommodate the patch of portal vein to which the splenic vein was attached. The host aorta was transected, and the spleen with its vessels was removed from the donor. The donor aortic segment was interposed between the severed ends of the host aorta, and the cuff of portal vein was sutured into place. Continuous No. 5-0 arterial silk was used for all vascular anastomoses.

The spleen was devascularized during transplantation for an average of 40 minutes. With release of vascular occlusion clamps, it became pink and firm and, in every instance, evidence of vascular flow through the organ was apparent. It was anchored by a few sutures to the lateral abdominal wall of the right lower quadrant to prevent torsion or kinking of the vessels. The recipient's own spleen was removed.

Total body irradiation (TBR) was administered to endotracheally intubated animals anesthetized with sodium pentobarbital. All animals were irradiated at a target skin distance of 140 centimeters. The area irradiated was 47 by 58 square centimeters. Dogs were placed on their sides and packed in a bolus of rice and flour in polyethylene bags. Filtration employed was one-half millimeter of copper plus 1 millimeter of aluminum. The half-value layer was 1.32 millimeters of copper. The tissue dose rate at the midplane was 15.4 roentgens per minute. Accuracy of dosage was checked periodically with a Farmer reference chamber.

Standard technique for white blood cell counts was employed. Microhematocrits were determined, and platlets were counted by the direct method.

Tissue for histologic study was obtained by either biopsy or sacrifice of animals just prior to death. Routine formalin fixation and hematoxylin and eosin staining were employed.

FIG. 2.

FIG. 3.

FIG. 2. Subcapsular infarction of spleen transplanted for 8 days. ×66.

FIG. 3. Hemorrhagic infarction of spleen evident 10 days after transplantation. ×53.

For study of the rejection of canine spleen homotransplants by the fluorescent antibody technique of Coons and Kaplan, portions of transplanted spleens and their arteries, as well as those from untreated controls, were quickly frozen on dry ice. The procedure employed was similar to that previously described by us in a report on the rejection of canine renal homotransplants (8). Sections cut in a cryostat were stained with antisera containing either antidog albumin or antidog fibrinogen which had been conjugated with fluorescein isocyanate. Sections similarly treated, except that they were first flooded with their respective nonfluorescent antisera, served as technical controls. Ultraviolet microscopy was performed using a mercury light source with appropriate exciter and barrier filters.

RESULTS

Spleen homotransplants in nonirradiated animals. Twenty dogs were the recipients of spleen homotransplants and removal of their own spleens. They were subjected to laparotomy and biopsy or removal of spleen at intervals of from 1 to 30 days after transplantation. After 7 days, all but 2 of the spleens examined demonstrated gross evidence of congestion and/or necrosis. The 2 animals demonstrating normal spleens at laparotomy 10 days after transplantation were re-explored, 1 at 20 and the other at 30 days. Both spleens were found to be extensively necrotic.

Microscopic sections of spleen obtained as early as 3 or 4 days after transplantation disclosed focal accumulations of neutrophils and deposits of fibrin in subcapsular sinusoids (Fig. 1). The malpighian bodies and red pulp appeared preserved, although the latter was frequently infiltrated with polymorphonuclear leukocytes. By 7 days after transplantation most spleens disclosed obvious necrosis of the subcapsular zone and varying degrees of hemorrhagic infarction

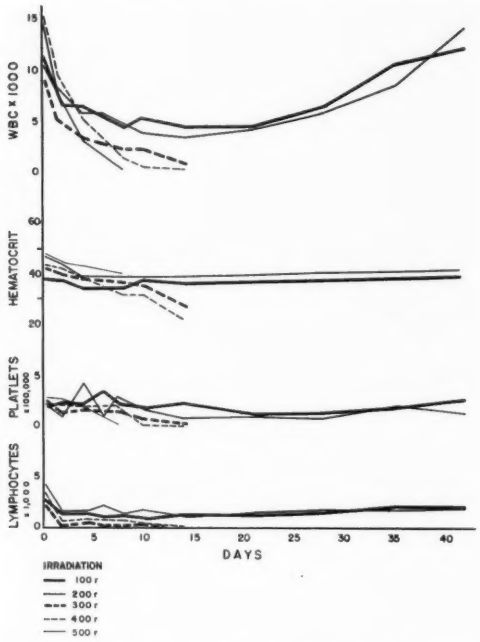


FIG. 4. Changes in total white blood cell count, hematocrit, lymphocytes, and platelets after varying doses of total body irradiation.

with only a scattering of lymphocytic elements (Fig. 2). Plasma cells and megakaryocytes were variable, and the subcapsular area contained a rim of neutrophils. Sections at later intervals, later than 10 days subsequent to transplantation, disclosed complete hemorrhagic infarction (Fig. 3). Focal necrosis of medium sized and small splenic arteries containing intramural deposits of fibrin, and occasionally thrombi, was also apparent in older transplants. Sections of the major branches of the splenic artery were without alteration.

TABLE I.—EFFECT OF TOTAL BODY IRRADIATION UPON SURVIVAL

Roentgen ray dosage, roentgens	*No. of dogs*	*Survived**	*Died*	*Survival, per cent*
100	10	9	1 (10 days)	90
200	6	6	0	100
300	12	1	11 (6 to 21 days)	8
400	6	0	6 (8 to 18 days)	0
500	6	1	5 (9 to 14 days)	17

*Longer than 6 weeks.

Spleen homotransplants in irradiated animals. To evaluate the dosage of total body irradiation upon animal survival, 40 dogs were subjected to between 100 and 500 roentgens. With the technique of irradiation employed, only 2 of 24 animals receiving 300 and 500 roentgens survived for 6 weeks (Table I), whereas of those receiving less than 300 roentgens only 1 of 16 died during this period of time. Changes in total white blood cell count, hematocrit, lymphocytes, and platelets (Fig. 4) in these animals were, in general, more pronounced the greater the dosage of irradiation.

Sections of spleen from animals subjected to 300 and 500 roentgens total body irradiation disclosed dimunition in size of malpighian bodies, the germinal centers of which were distinctly atrophic or absent. Varying amounts of hemosiderin, lying free as well as in macrophages, were evident throughout the red pulp (Fig. 5). Sections of bone marrow revealed severe hypoplasia and, in many instances, aplasia of hemopoietic elements. The lungs frequently disclosed marked congestion and edema. On occasion, bacterial masses could be identified within capillary loops of glomeruli and the lumens of interstitial capillaries; otherwise, the renal architecture appeared well preserved. Focal mucosal ulceration was observed in sections of the small and large intestine. Livers showed moderate central congestion. Sections of heart, adrenals, and pancreas were without pathologic change.

Because of the almost 100 per cent lethality of 300 and 500 roentgens of total body irradiation, these dosages were selected for administration to 12 animals prior to spleen homotransplantation. Of the 5 dogs receiving 300 roentgens 1 died at 9, 2 at 10, and 1 at 18 days; 1 was sacrificed 42 days after transplantation. All 7 animals that received 500 roentgens died between 7 and 14 days after irradiation, at 7, 10, 11, 11, 14, 14, and 14 days. The spleens in 9 of the 12 animals

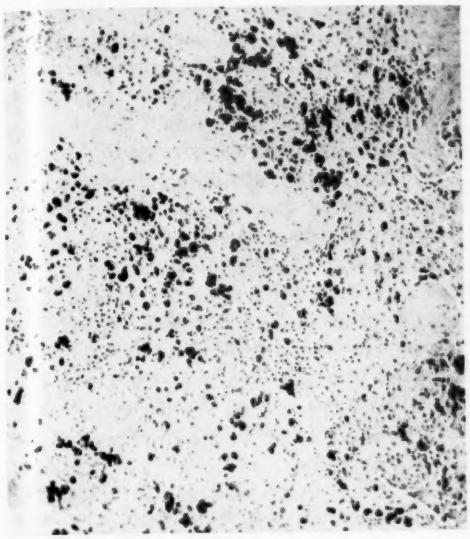


FIG. 5.

FIG. 6.

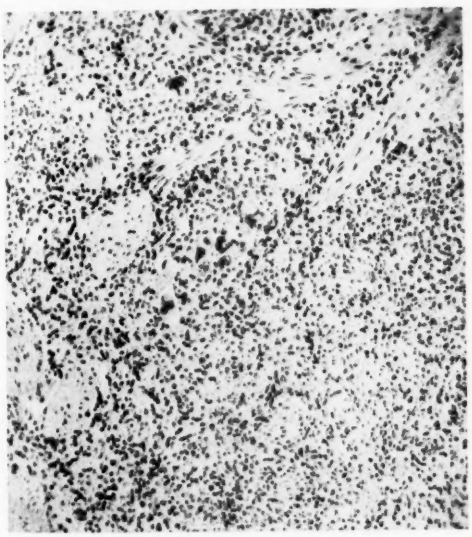


FIG. 7.

FIG. 8.

FIG. 5. Photomicrographic appearance of spleen from irradiated dog disclosing markedly diminished lymphoid elements and hemosiderin laden macrophages which appear black. ×55.

FIG. 6. Photomicrograph shows normal appearing spleen 14 days after transplantation in dog subjected to total body irradiation. ×53.

FIG. 7. Photomicrographic appearance of focus of megakaryocytes in splenic transplant of irradiated dog. ×88.

FIG. 8. Photomicrographic appearance of splenic transplant of irradiated dog 14 days after transplantation resembling that depicted in Figure 2 from nonirradiated animal. ×53.

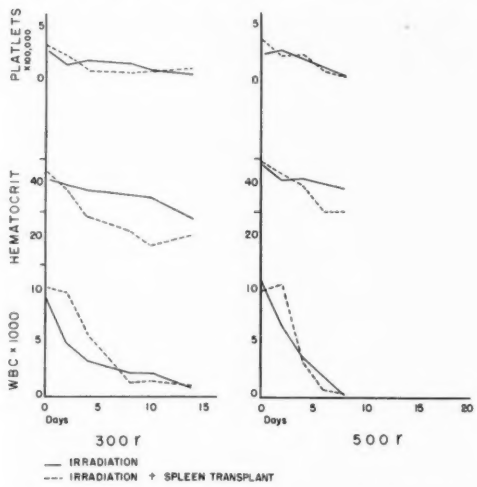


FIG. 9. Comparison of changes in white blood cell count, hematocrit, and platelets between dogs irradiated and irradiated with spleen transplants.

appeared grossly normal. The microscopic appearance of spleens transplanted after total body irradiation was that of normal architecture for as long as 14 days after transplantation (Fig. 6). In only one were there small focal subcapsular deposits of fibrin. The number of immature and mature megakaryocytes within the spleen appeared to be greater than that observed in normal controls (Fig. 7). In no instance were other immature hemopoietic elements indicative of extramedullary hemopoiesis observed. The spleens removed subsequent to 14 days after transplantation showed varying degrees of hemorrhagic infarction and autolysis characterized by loss of splenic architecture, massive hemorrhage, and a variable infiltrate of neutrophils (Fig. 8). Plasma cells were not conspicuous. Sections prepared from sternal bone marrow, lungs, myocardium, adrenals, and liver disclosed changes similar to those observed in dogs subjected to total body irradiation only.

Dogs with homotransplanted spleens after irradiation did not show a marked difference in white blood cell or platelet count from those with irradiation alone (Fig. 9). A greater drop in hematocrit did occur.

Fluorescent antibody after splenic homotransplantation. Portions of spleen were obtained by biopsy 3 and 4 days after transplantation as well as at sacrifice of animals with splenic transplants of 7, 10, 14, and 21 days' duration. In no instance was preferential localization of gamma globulin observed. The fluorescence of gamma globulin in the lumen of splenic vessels, zones of splenic necrosis, and in the cytoplasm of plasma cells and reticulum cells of splenic transplants appeared to be of the same magnitude as that observed in these loci in normal spleens. Albumin and fibrinogen (Fig. 10) were identified within these sites in both normal and transplanted spleens.

DISCUSSION

Since death or specific clinical manifestations are not sequelae of spleen rejection, laparotomy and/or biopsy must be performed to determine its status. Attempting to circumvent the need for repeated operative procedures, we resorted to the use of roentgenography with thorotrast, spleen scanning after the injection of radioactive chromium (Cr^{51}) tagged red blood cells, and complete blood counts, including platelets—all with little success.

The histologic findings noted in the spleen after homotransplantation closely resemble those observed in renal transplant rejection. The earliest changes seen were deposits of fibrin in the subcapsular vessels and neutrophil infiltration. Small areas of subcapsular necrosis progressing to complete infarction subsequently occurred, suggesting that rejection proceeds inward from the capsular surface. Although thrombi in sinusoids appear as the earliest change, vasculitis and thrombi in larger vessels were noted subsequent to initial infarction.

It was fully appreciated that, with the dosage of irradiation employed, permanent or at least markedly prolonged suppression of host response to the homograft would not result. It was necessary for Ferrebee and associates to administer 1,200 roentgens of total body irradiation to a dog before a

homografted marrow cell survived, and more recently, Hume and associates reported that only after 1,500 roentgens was the typical rejection phenomenon usually seen in renal transplants prevented. It was hoped, however, that with the dosage of irradiation employed, 300 to 500 roentgens, there would at least be a delay in rejection to or beyond the time at which a control series of animals were found to die from the effects of the irradiation. This was observed. By 14 days, when 80 per cent of the control animals which had received 300 to 500 roentgens total body irradiation (TBR) had died, 75 per cent of the spleens which had been transplanted into animals after such dosages of TBR were histologically still good, with little or no evidence of rejection. No prolongation of survival was effected, however, in this group. Just as in the control group, almost all animals were dead by 2 weeks as a result of the irradiation.

Thus, from this study it seems unlikely that the spleen elaborates a humoral factor which is protective against the lethality of irradiation. It is reasonable that, if such were so, a maximum effect would be discernible under the conditions of these experiments. That the production of such a factor is impaired by the procedure of transplantation, i.e., anoxia, remains but a remote possibility when one considers the techniques employed by those who have favored such a mechanism.

Aside from observing more megakaryocytes in the transplanted spleens than normally seen, no evidence of hematopoiesis was noted. Our attempts to transplant newborn puppy spleens which are hematopoietically active have been technically unsuccessful. It would seem that the mechanism of protection against irradiation lethality afforded by spleen as reported by numerous investigators is most likely related to "cellular repopulation" and/or a temporary activity of administered cells pending recovery of the recipient marrow.

The failure to demonstrate any preferential localization of gamma globulin in the spleen transplants using the fluorescent antibody technique is similar to our findings after renal homotransplant. Although this finding is consistent with the failure of most investigators to detect circulating antibodies in the rejection phenomenon, as we have previously stated this does not unequivocally exclude their presence. The antibody might be in such low concentration or with such little avidity that it remains undetected. Also, the findings do not exclude the presence of tuberculin or cellular hypersensitivity type.

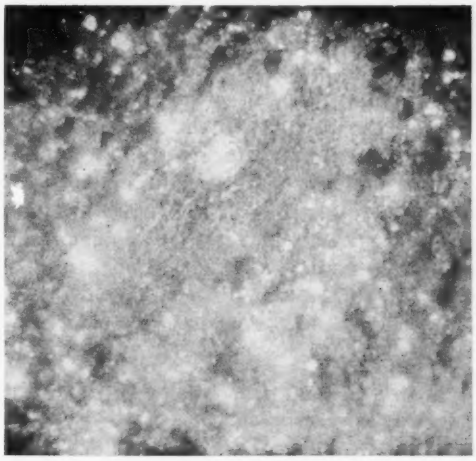


FIG. 10. Section of splenic transplant 4 days after transplantation stained with antidog fibrinogen revealing white fibrin deposits. ×80.

SUMMARY AND CONCLUSIONS

Spleen homotransplantation was carried out with the purpose of: (a) documenting the histologic fate of such transplants; (b) evaluating the mechanism whereby splenic tissue affords protection against total body irradiation; and (c) employing the fluorescent antibody technique to gain information concerning the homotransplantation rejection phenomenon.

The histologic pattern of rejection, in many ways, resembles that seen after kidney homotransplantation. The earliest changes to be observed were deposits of subcapsular fibrin with subsequent necrosis and hemor-

rhagic infarction. No preferential localization of gamma globulin was noted during the rejection process.

The protective effect of splenic tissue against radiation lethality is more likely due to "cellular repopulation" than to a humoral factor. Animals receiving lethal doses of irradiation and subsequent spleen homotransplantation survived no longer than control animals, although at the time of death the transplanted spleens were grossly and microscopically normal.

REFERENCES

1. Allen, B. R., Wardell, H. G., and Clay, M. Postirradiation protection of rabbits by injection of splenic plasma. Science, 1956, 123: 1080.
2. Brown, M. B., Hirsch, B. B., Nagareda, C. S., Hochstetler, S. K., Farraghan, W. G., Toch, P., and Kaplan, H. S. Some biological aspects of the factor in bone marrow responsible for hematopoietic recovery following systemic irradiation. J. Nat. Cancer Inst., 1955, 15: 949.
3. Cole, L. J., Fishler, M. C., and Bond, V. P. Subcellular fractionation of mouse spleen radiation protection activity. Proc. Nat. Acad. Sc. U. S., 1953, 39: 759.
4. Cole, L. J., Fishler, M. C., Ellis, M. E., and Bond, V. P. Protection of mice against x-irradiation by spleen homogenates administered after exposure. Proc. Soc. Exp. Biol., N. Y., 1952, 80: 112.
5. Coons, A. H., and Kaplan, M. H. A study of the localization of antigen in tissue cells—II, improvements in a method for the detection of antigen by means of fluorescent antibody. J. Exp. M., 1950, 91: 1.
6. Ellinger, F. Further studies with cell-free extracts from mouse spleen on x-ray induced mortality. Proc. Soc. Exp. Biol., N. Y., 1956, 92: 670.
7. Ferrebee, J. W., Lochte, H. L., Jr., Jaretzki, A., III, Sahler, O. D., and Thomas, E. D. Successful marrow homograft in the dog after radiation. Surgery, 1958, 43: 516.
8. Fisher, E. R., and Fisher, B. Investigation of rejection of canine renal homotransplants by the fluorescent antibody technic. Proc. Soc. Exp. Biol., N. Y., 1959, 101: 259.
9. Hume, D. M., Jackson, B. T., Zukoski, C. S., and Egdahl, R. H. The homotransplantation of kidney and of fetal liver after total body irradiation. Ann. Surg., in press.
10. Jacobson, L. O. Evidence for a humoral factor (or factors) concerned in recovery from radiation injury; a review. Cancer Res., 1952, 12: 315.
11. Jacobson, L. O., Marks, E. K., Rolson, M. J., Gaston, E. O., and Zirkle, R. E. The effect of spleen protection on mortality following x-irradiation. J. Laborat. Clin. M., 1949, 34: 1538.
12. Jacobson, L. O., Simmons, E. L., Marks, E. K., Gaston, E. O., Rolson, M. J., and Edredge, J. H. Recovery from radiation injury. Science, 1951, 113: 510.
13. Kaplan, H. S. On the etiology and pathogenesis o the leukemias; a review. Cancer Res., 1954, 14: 535.
14. Loutit, J. F. Protection against ionizing radiation. The "recovery factors" in spleen and bone marrow. J. Nuclear Energy, 1954, 1: 87.
15. Savitsky, J. P. Control of radiation hemorrhage with splenic extracts. Blood, 1955, 10: 52.

AN EXPERIMENTAL STUDY OF THE INFLUENCE OF PORE SIZE OF IMPLANTED POLYURETHANE SPONGES UPON SUBSEQUENT TISSUE FORMATION

J. E. SALVATORE, M.D., W. S. GILMER, JR., M.D., MARK KASHGARIAN, M.D., and W. RALPH BARBEE, B.S., Memphis, Tennessee

IN THE LAST 15 YEARS the literature on the use of various plastics as prosthetic material has grown enormously, and several new areas of study within this field have been defined. One of these is the identification and definition of the basic tissue reactions which develop after the introduction of these plastic materials into living tissue and the influence of the physical structure of the introduced material upon the kind and quality of tissue subsequently formed. For example, Oppenheimer and associates (4, 5) have shown that the physical configuration of a particular plastic may be of paramount importance with regard to carcinogenesis. Nothdurft has suggested that implantations in the form of thin plates are more carcinogenic than are perforated plates or powder.

In 1949, Grindlay and Clagett reported the use of polyvinyl alcohol sponge, ivalon®, as a framework for living tissue, and it has been found to support the growth of new tissue with a minimal foreign body reaction. Our related studies (6) and those of Marzoni and associates have shown that other spongy or porous plastics, e.g., polyurethane, and silicone share this property. The present study explores the effect of variation in the pore size of plastic sponge upon the formation of new connective tissue.

MATERIALS

Our purpose required a plastic sponge in which pore size could be both varied and standardized with some accuracy. Polyurethane polymer met this requirement. With this plastic it is also possible to produce pores that are either "open"—communicating with adjacent pores—or "closed"—isolated from adjacent cells by pore walls. Of the open form, 6 pore sizes were chosen; the smallest had 90 pores per linear inch, the largest, 8 pores. These were arbitrarily numbered in ascending order of pore size from 1 to 6 (Fig. 1a to f). From 6 large sponges, one of each pore size, blocks were cut measuring 1 by ¾ by ¼ inch, 30 from each sponge, a total of 180 sponges for implantation. Ninety mature female rats of the Sprague-Dawley strain weighing from 200 to 300 grams each were used. Two sponges of differing pore size were implanted in each.

METHOD

Each rat was anesthetized with ether. A longitudinal midline incision 2 inches long was made in the skin of the abdominal wall, and dissection was carried out through the subcutaneous space to the right and left of the midline for about 2 inches on each side. Two sponges were inserted, one on the right and one on the left, making certain that they lay flat and were not folded upon themselves. The incision was closed with interrupted sutures of No. 000 silk. The medial edge of each sponge was from ¼ to ½ inch from the midline and its greatest dimension was parallel to the long axis of the animal.

After this procedure the animals were given penicillin and streptomycin and main-

From the Campbell Foundation and the Division of Pathology and Microbiology, University of Tennessee Medical Units, Memphis.

This study was supported by Grant No. A 1073-C4 from the National Institutes of Health.

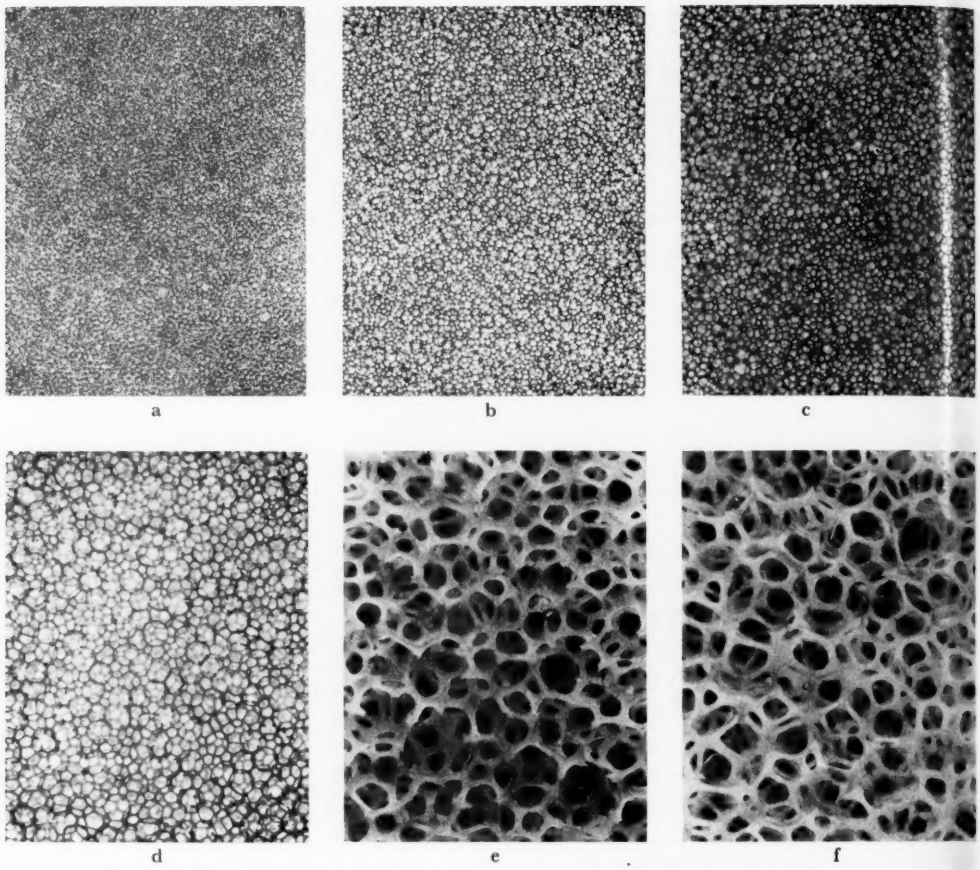


FIG. 1. Photographs of the 6 sponges of varying pore size. × 2. a, Size 1; b, size 2; c, size 3; d, size 4; e, size 5, and f, size 6.

tained on a supply and demand diet of standard purina rat chow. They gained weight and maintained a healthy appearance. Infection was subsequently noted in 2 sponges, one in each of 2 animals; they were discarded, leaving 178 for analysis.

Five groups of 18 rats each were sacrificed at intervals of 1, 2, 3, 4, and 8 weeks. The sponges were then harvested. Tags of tissue not conforming to the shape of the sponges were discarded, and care was used to exclude areas of muscle and fascia. The yield was 6 sponges of each pore size at each time interval. One of these was used for histologic study, tissue sections being cut from the midportion of each and prepared by the conventional methods. The other sponges were used for studies of water content. They were weighed wet after excision, desiccated in a vacuum oven at 100 degrees C., and again weighed dry; weights were compared with each other and with preimplantation weights.

STATISTICAL RESULTS

The data on the wet and dry weights of the sponges as compared with preimplantation weights were subjected to many statistical analyses, but the significance of this part of our study is uncertain and is not being reported at this time.

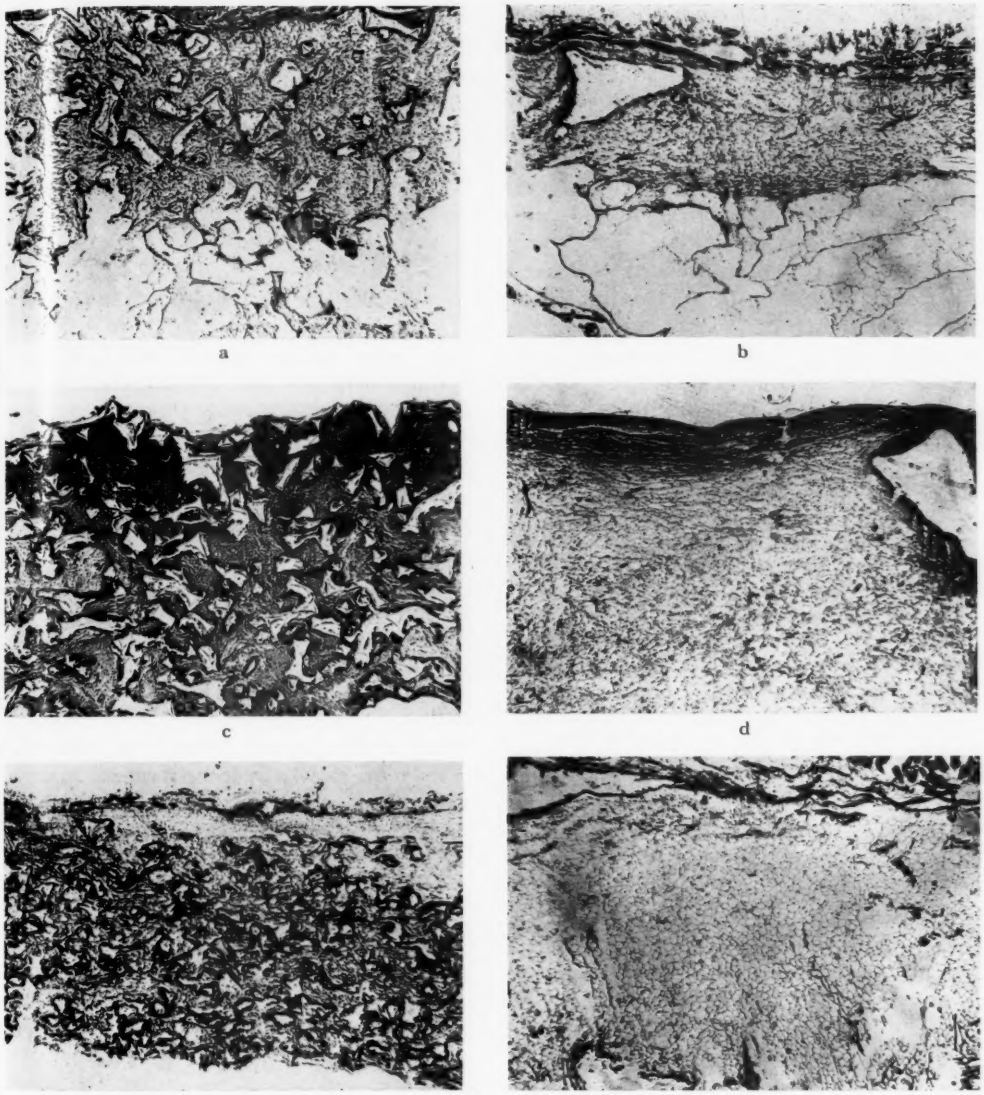


FIG. 2. Photomicrographs illustrating the tissues filling sponges of pore sizes 1 and 6 at 1, 4, and 8 weeks. × 7.6. a, Pore size 1 at 1 week. The sponge is more than half filled by moderately cellular fibroblastic tissue. One periphery of the sponge is at the upper margin of the picture. The trabeculae are seen as variously shaped spicules with pointed extremities lying in the empty spaces. b, Pore size 6 at 1 week. Sparsely cellular, loose-meshed tissue is seen filling the periphery of the sponge. At the upper margin of the picture is a layer of fascia which was contiguous to the surface of the sponge. Delicate strands of fibrin can be seen within the empty spaces in the sponge. c, Pore size 1 at 4 weeks. The pores of the sponge are completely filled by dense collagenous tissue in which focal areas of vacuolization may be seen. d, Pore size 6 at 4 weeks. The sparsely cellular, areolar tissue filling the interstices of the sponge is demonstrated. This closely resembles that seen at 8 weeks. Moderate collagen formation about a single trabecula is seen in the upper right corner. e, Pore size 1 at 8 weeks. Diffuse vacuolization of the collagenous tissue is seen. The marked shrinkage of the sponge, so that both surfaces are visible in the photograph, is apparent. f, Pore size 6 at 8 weeks. The apparently mature areolar tissue fills the sponge.

HISTOLOGIC OBSERVATIONS

Pore sizes 1 and 2 (Figs. 2a, c, and e, and 3a, c, and e). In sponges of pore sizes 1 and 2 there was a rapid filling by a moderately cellular, moderately vascular mesenchyme in which collagen formation proceeded rapidly and abundantly. Although scattered lymphocytes were seen, no acute inflammatory reaction was observed. There was a delicate fibrin clot containing scattered mononuclear cells in the pores not filled by tissue. A striking foreign body reaction developed about the trabeculae of these sponges, became maximal within 2 weeks, and then subsided, but persisted in some degree for the duration of the experiment. Filling of the pores was virtually completed in 2 weeks and entirely so in 3 weeks. Considerable vacuolization then developed within the collagenous tissues, at first focally and at random, later generally, so that the tissue was less dense at 8 weeks than it had been at 4 weeks and did not resemble an ordinary scar. Associated with the filling, and most marked after filling was complete, was a progressive decrease in the size of the sponges.

Pore sizes 5 and 6 (Figs. 2b, d, and f and 3b, d, and f). In contrast, the sponges of the largest pore sizes were filled by less vascular and cellular tissue, from which gross collagen formation was absent except for occasional small areas adjacent to a trabecula. Isolated strands of fibrin and mononuclear cells were seen in the spaces not occupied by the tissue. The filling was accomplished much more slowly than in pore sizes 1 and 2, after 4 weeks instead of 2 weeks, but the tissue filling the pores was essentially mature tissue even at 2 weeks and underwent minimal differentiation to resemble mature areolar tissue. There was no significant difference in the histologic characteristics of this tissue at 3 and at 8 weeks. There was some decrease in the size of the sponges but not nearly so marked as in pore sizes 1 and 2.

Pore sizes 3 and 4. The changes in these sponges were more or less intermediate in character but ultimately much more like those of the largest pore sizes. There was some collagen formation and a moderate foreign body reaction about the trabeculae which subsided in 3 or 4 weeks. At 8 weeks the pores were filled by loose-meshed areolar tissue and in no instance was any significant collagen formation observed deep within the interstices.

DISCUSSION

The striking differences in the tissue filling the interstices of the sponges of smallest pore size when compared with that filling the sponges of largest pore size demonstrate that the spatial arrangement of the sponges considerably influenced the type of tissue filling them. In addition, the difference in the time required for these two dissimilar tissues to accomplish this filling must be regarded as significant.

In the sponges of pore sizes 1 and 2 fibroplasia proceeded quite rapidly and by 2 weeks they were filled by a dense, apparently mature collagen. The subsequent appearance of vacuoles in this tissue probably was due to imbibition of water. On the other hand, the sponges of largest pore size were filled more slowly by loose-meshed, sparsely cellular, areolar tissue which underwent only slight differentiation during the course of the experiment.

It was clear that the trabeculae of the smaller sponges acted as foreign bodies; this reaction was seen only rarely and to a minimal degree in the larger sponges. This difference was probably related to the difference that was noted in the size of the trabeculae.

It certainly was to be expected that organization of the fibrin clot within the sponges would have taken place in the usual manner. But the expected sequence of granulation tissue proliferation progressing to scar formation was not observed. There was no inflammatory reaction, other than the foreign body reaction, and no tissue resembling either granulation tissue or scar within the usual meaning of these words was seen.

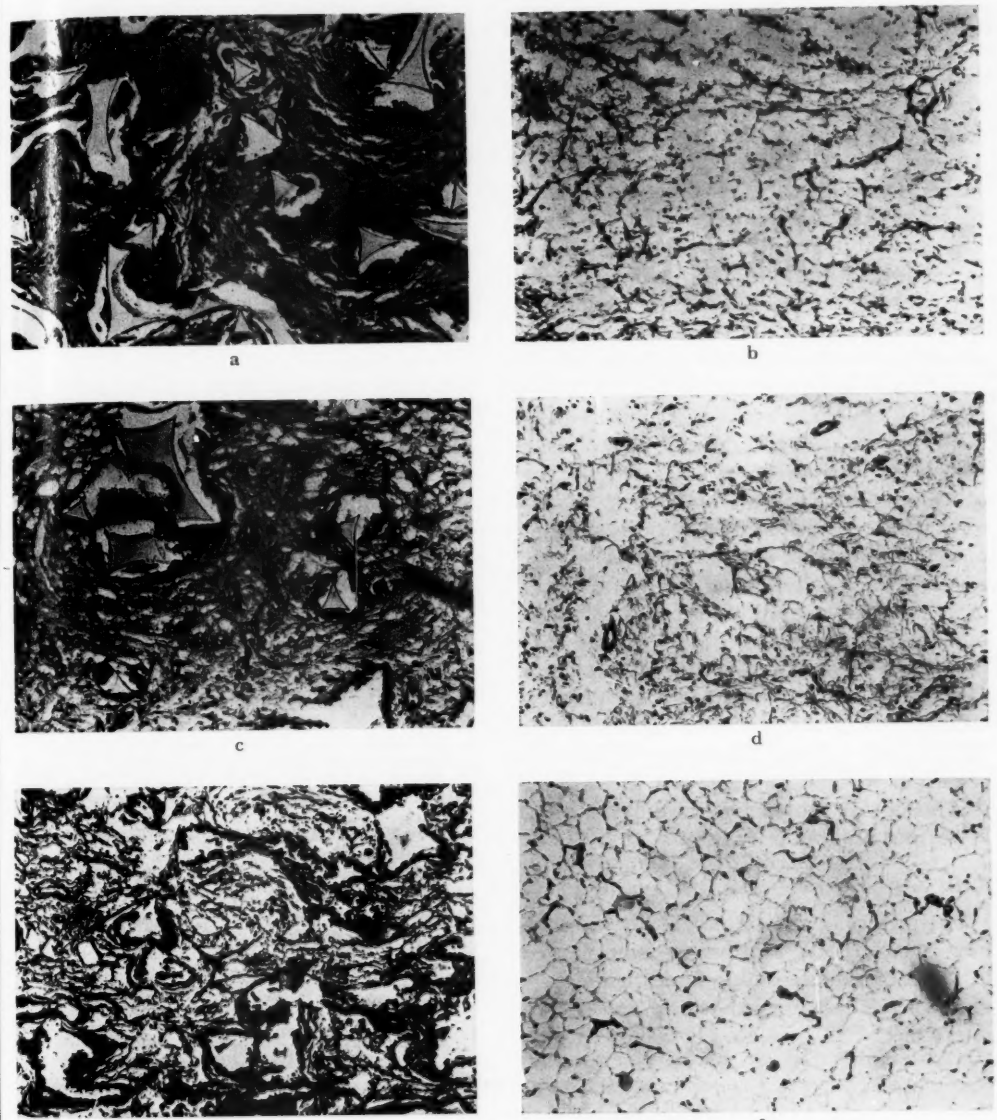


FIG. 3. Photomicrographs illustrating in detail the tissues occupying the sponges of pore sizes 1 and 6 at 1, 4, and 8 weeks. × 26. a, Pore size 1 at 1 week. The pores are filled by heavily collagenized tissue, and a striking foreign body reaction is seen about the trabeculae. b, Pore size 6 at 1 week. The tissue filling the sponge has a delicate reticular character and there is little discernible collagen formation. c, Pore size 1 at 4 weeks. This photomicrograph illustrates the beginning vacuolization of the collagenous tissue which has filled all pores of the sponge. The foreign body reaction persists. d, Pore size 6 at 4 weeks. This photomicrograph demonstrates the relatively mature areolar tissue which at this time has filled all the spaces of the sponge. e, Pore size 1 at 8 weeks. Here, the fairly extensive vacuolization that has occurred is illustrated. Dense masses of collagen persist about the trabeculae, still associated with some foreign body giant cells. f, Pore size 6 at 8 weeks. The tissue filling the sponge at this time is apparently mature areolar tissue.

It may be proposed that the differences described represent in the small pored sponges a florid foreign body reaction and in the large pored sponges a gradual oozing or flowing of areolar tissue into the larger sponges. This explanation does not account for all the differences. We believe a more reasonable interpretation is that the tissue filling the sponges is properly designated as mesenchyme, and that the rate of formation and degree or type of differentiation are influenced by the spatial arrangement of the structure within which the changes occur.

If this interpretation is correct, if indeed the physical framework upon which tissue forms may so alter the ultimate type of tissue formed, then we are inevitably led to some speculation as to the importance of this observation in fields such as bone grafting and the prosthetic replacement of various organs. Many different materials have been used to support or promote fibrogenesis—bone, plastics, and plaster of paris, for example—and all with varying degrees of success. One wonders what the general physical structure of the material used had to do with its ultimate efficacy. Presently we are engaged in further investigation to evaluate this particular property in various materials in various anatomic locations.

SUMMARY

Sponges of open cell polyurethane polymer of different pore sizes were implanted in the subcutaneous abdominal tissue of 90 mature female rats and were harvested at intervals of 1, 2, 3, 4, and 8 weeks.

Very striking differences in the tissues filling the interstices of the sponges of different pore sizes were observed. The smallest pores were rapidly filled by a dense collagenous tissue which subsequently underwent some vacuolization apparently as a result of imbibition of water. In contrast, the sponges of largest pore size were filled much more slowly with a loose-meshed areolar tissue which underwent very little further differentiation during the course of the experiment.

It is believed that this experiment indicates that the physical structure, specifically the pore size, of the plastic sponge exerts a considerable influence upon the type of tissue formed and the rate of filling, and further studies to evaluate this phenomenon in other connective tissues are in progress.

REFERENCES

1. Grindlay, J. H., and Clagett, O. T. A plastic sponge prosthesis for use after pneumonectomy; preliminary report. Proc. Mayo Clin., 1949, 24: 538–539.
2. Marzoni, F. A., Upchurch, S. E., and Lambert, C. J. An experimental study of silicone as a soft tissue substitute. Plastic & Reconstr. Surg., 1959, 24: 600–608.
3. Nothdurft, H. Ueber die Sarkomausloesung durch Fremdkoerperimplantationen bei Ratten in Abhangigkeit von der Form der Implantate. Naturwissenschaften, 1955, 42: 106.
4. Oppenheimer, B. S., Oppenheimer, E. T., and Stout, A. P. Carcinogenic effect of imbedding various plastic films in rats and mice. Surgical Forum 1952; American College of Surgeons. Vol. III, pp. 672–676. Philadelphia and London: W. B. Saunders Co., 1953.
5. Oppenheimer, B. S., Oppenheimer, E. T., Stout, A. P., and Danishefsky, I. Malignant tumors resulting from imbedded plastics in rodents. Science, 1953, 118: 305–306.
6. Salvatore, J. E., and Mandarino, M. P. Polyurethane polymer, its use in osseous lesions; an experimental study. Ann. Surg., 1959, 149: 107–109.

ASSESSMENT OF THE EXFOLIATION OF TUMOR CELLS INTO THE BODY CAVITIES

GEORGE E. MOORE, M.D., F.A.C.S., KUMAO SAKO, M.D., TATSUHEI KONDO, M.D., JORGE BADILLO, M.D., and EUGENE BURKE, B.S., Buffalo, New York

THE PRESENCE of tumor cells in the peritoneal fluids from patients with cancer has been studied and reported at intervals since 1867, when Lücke and Klebs published their observations on ascitic fluid from patients with malignant tumors of the ovary. In recent years, however, the problem of cancer cell spillage, dissemination, and implantation has provoked increasing interest and speculation regarding the clinical significance of finding unestablished tumor cells in the peritoneal cavity at the time of operation.

Pomeranz and Garlock reported in 1955 that positive smears were recovered from the serosa in 2 of 20 cases of carcinoma of the colon in which the tumor had invaded the full thickness of the intestinal wall. These investigators commented on the grave danger of dissemination and implantation within the peritoneal cavity of malignant cells exfoliated from serosal surfaces.

Keettel and Elkins performed routine peritoneal washings in 275 gynecologic cases. Of 20 patients with malignant ovarian tumors, 13 had smears containing positive or suspicious cells. In 5 of these patients there was no evidence of spread beyond the ovary, but tumor cells were present in the washings. The findings in these cases suggested that the poor prognosis of patients with no visible evidence of local or distant tumor cell spread may be associated with the exfoliation of cells into the peritoneal cavity. These investigators recommended the use of radioactive colloidal gold for the destruction of such cells.

From the Departments of Surgery and Pathology, Roswell Park Memorial Institute, Buffalo.

Supported by U. S. Public Health Service Grants CY-3435-C2 and CY-3553-C2.

Spjut and his associates collected 60 pleural cavity washings at the time of operation. Of the 49 patients with lung cancer, 16 (33 per cent) had specimens containing cancer cells. Cancer cells were present in pleural washings from 10 of 28 patients undergoing pneumonectomy or lobectomy.

Quan assayed the cul-de-sac fluid of patients with carcinoma of the colon and rectum by preparing smears directly from swabs. Among the 133 specimens considered technically suitable for study, there were 33 positive slides, 40 suspicious, and 60 negative. There were only 2 false positive slides and 4 false suspicious. The most interesting findings were 15 negative smears from patients with visible intraperitoneal metastases, and 8 positive smears from patients without evidence of abdominal metastases.

Our staff has obtained routine washings of the peritoneal cavity before and after operative manipulation since 1956 (4, 5). The results of this study to date form the basis of this report.

METHOD

Routine washings of the peritoneal cavity both before and after operative manipulation were obtained in all instances except when only a single specimen was obtained, as in exploratory celiotomy without further operation. The simple technique used in the study consisted of spraying 20 cubic centimeters of saline against the viscera and peritoneal surfaces adjacent to the tumor and aspirating the fluid from the gutters or cul-de-sac, using a long curved aspirating syringe with a rubber bulb. With care, an average of 12 cubic centimeters of fluid is recoverable. The fluid was sent immediately to the

TABLE I.—PERITONEAL WASHINGS IN RELATION TO CURABILITY

Location of lesions	Washings: Curable cases: Positive	Curable cases: Neg.	Curable cases: Atypical	Noncurable cases: Positive	Noncurable cases: Neg.	Noncurable cases: Atypical	Total No. cases
Stomach	10(32)	20	1	26(59)	18	0	75
Colon	18(23)	54	5	20(47)	22	1	120
Rectum	11(12)	74	4	18(35)	29	5	141
Ovary	6(67)	3	0	44(75)	13	2	68
Uterus	18(23)	58	3	19(46)	21	1	120
Cervix	21(15.4)	109	6	24(36)	39	4	203
Totals	84(20.0)	318	19	151(49.3)	142	13	727

Figures in parentheses are percentages.

TABLE II.—COMPARISON OF WASHES OF PERITONEAL CAVITY AT BEGINNING AND END OF OPERATION

Location of lesions	Washings: Pos.→Pos.	Pos.→Neg.	Neg.→Pos.	Neg.→Neg.
Stomach	14	5	10	33
Colon	20	7	7	61
Rectum	12	8	3	93
Ovary	28	10	8	13
Uterus	8	13	10	66
Cervix	10	22	6	127

TABLE III.—CURABLE CASES

Location of lesions	Washings: Positive pathologically: +	Positive pathologically: −	Negative pathologically: +	Negative pathologically: −	Total
Stomach	10	14	0	6	30
Rectum	7	35	4	39	85
Colon	15	36	4	17	72
Ovary	2	3	3	1	9
Uterus	4	6	14	52	76
Cervix	4	20	17	89	130
Totals	42	114	42	204	402

cytology laboratory and centrifuged, and multiple smears were made of the centrifugate. Both Wright-Giemsa and Papanicolaou preparations were used. The former slides were screened by two of us and rechecked by a third; the latter slides were screened by cytology technicians and checked by the senior cytologist. Independent reports were prepared, and a final diagnosis was registered.

Cytologic and histologic aspects. There is little question that a cytologist experienced in examining different kinds of cellular specimens is paramount for such studies as these. The preparations contain exfoliated cells from various tissues, mesothelial cells altered by inflammation, irradiation, or trauma, and bizarre neoplastic cells.

The cytologic details of neoplastic cells will not be reviewed here, but the observer should be warned of the manifold appearances of mesothelial cells. Despite histochemical analyses and supravital and fluorescent staining techniques, there still remain altered mesothelial cells which closely mimic malignant cells.

In this study, all slides marked positive by either cytology group were confirmed by the other group. Patients with benign disease were included and were used as controls. For the purposes of this report, all patients were classified as either curable, with complete excision of all gross tumor, or incurable.

Sampling errors in such a study are probably large. They may result from any of the following factors: (1) the residents' enthusiasm or lack of it for the performance of the washings; (2) the use of too much saline, so that only a fraction of it is recovered, thus effectively reducing the number of cells available for the smears; (3) an excessive amount of blood, which obscures the tumor cells; (4) the time relationship of the postsurgical manipulation of the specimen to removal of the mass; and (5) sampling errors in making the smear preparations from the centrifugate.

RESULTS

The observations reported in the present study include those on 727 surgical patients with malignant disease of the stomach, colon, rectum, ovary, uterus, and cervix and on 106 surgical patients with benign lesions.

A known false positive diagnosis was made in 9 of the 106 nonmalignant cases. These data are given first so that the relative accuracy of the method can be appreciated before the specific studies are summarized.

In 4 of the 9 false positive cases, only 1 washing was considered positive; but in the other 5 cases, both washings from each case were diagnosed as containing malignant cells. The actual diagnoses in these cases were benign gastric ulcer, gastritis, diverticulitis of the sigmoid, and papillary serous cystadenoma of the ovary. The patient with

2 positive washings and a final pathologic diagnosis of papillary serous cystadenoma of the ovary is noteworthy. At celiotomy, large bilateral ovarian tumors were found (Fig. 1). The tumor masses had to be manipulated in order to effect removal, and a cyst was ruptured in the process. This may have been the cause of the plethora of malignant-like cells which resembled typical ovarian or malignant mesothelial cells (Fig. 2).

The frequency of false positive diagnoses for patients with confirmed malignant disease may be slightly greater, as such patients often have inflammatory changes, postirradiation reactions, or intestinal obstruction, any of which may provoke exfoliation of benign cells with altered structure. The extent of false negative errors is difficult to assess. Some estimate of such errors can be seen by noting that among 143 patients with either peritoneal implants or ascitic fluid, the washings were positive in 96 cases, contained atypical cells in 5, and were negative in 42. Some negative washings are to be expected in such instances, since no cancer cells can be isolated from ascitic fluid in some cases, even when the patients have massive amounts of ascites associated with malignant lesions.

Relationship of disease status to cell washings. Table I lists the results of peritoneal washings according to curability. It is evident that the frequency of positive washes in curable cases is less than in those that are incurable. The percentage of positive washings is high for gastric lesions that are resectable but advanced. The following case report exemplifies this finding.

A 59 year old white male underwent an operation on 29 October 1957 for a lesion of the cardia of the stomach. The lesion was 12 centimeters in diameter but did not involve adjacent structures except for a small area of adherence to the body of the pancreas. A total gastrectomy, with partial pancreatectomy, omentectomy, and splenectomy, and an esophagojejunostomy, was performed. Pathologic examination of the specimen revealed serosal involvement, metastases to the regional nodes, and extension into the adherent portion of the pancreas. The peritoneal washings were positive at the beginning of operation and again at the end (Fig. 3). Extensive peritoneal implants developed and the patient died 2 months after operation.

FIG. 1. Bilateral papillary serous cystadenoma of the ovary.

Effect of surgical procedure. Washings obtained at the beginning and at the end of the exploratory celiotomy are compared in Table II. The patients with atypical cells and those with only 1 washing were omitted from the table. These comparisons suggest the approximate size of the sampling errors in obtaining equivalent washings.

The results obtained in this study provide no clear-cut support of the thesis that cancer cell spread into the body cavity is increased by surgical manipulation, except perhaps in the patients with gastric cancer. In the groups with disease of the stomach and ovary, the majority of patients becoming positive after manipulation were those undergoing palliative procedures.

Transtubal exfoliation of uterine carcinoma. There is little agreement on the frequency of transtubal spread as the source of peri-

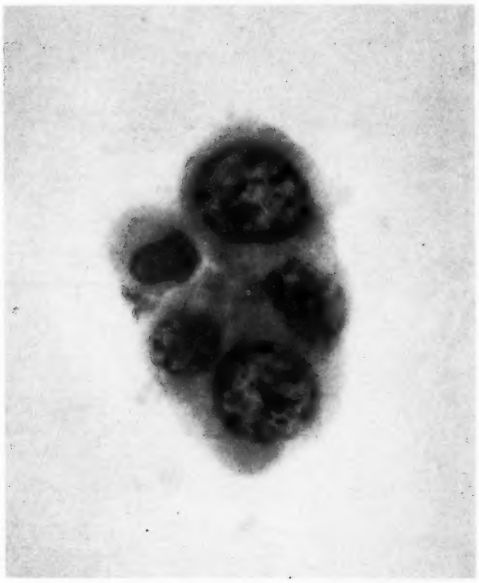


FIG. 2. Malignant-like cells from peritoneal washings in a case of papillary serous cystadenoma of the ovary.

toneal metastases in endometrial carcinoma confined to the uterus. Dahle found 11 of 21 patients with carcinoma of the body of the uterus to have tumor cells in either one or both tubes. In 7 cases, tumor cells were recovered from the cul-de-sac.

In our series of 66 cases with no evidence of serosal involvement, metastases, peritoneal seeding, or ascites, there were 14 cases, 21 per cent, with positive washings recovered from the cul-de-sac. This is a significant enough number to lend support to the possibility of transtubal spread. It must be remembered, however, that we have obtained positive washings from other kinds of malignant lesions in which serosal invasion was not present. In view of the frequency of intraperitoneal metastases, these cells must be considered as a possible etiologic factor in the development of metastases, despite the difficulty of confirming the viability of these cells.

Significance of peritoneal washings as a prognostic guide. The 402 curable patients, excluding the 19 atypical ones, were divided into two groups: those with at least one kind of positive pathologic finding, such as metastases, serosal invasion, implants, or ascites, and those with completely negative pathologic findings. The results are listed in Table III.

Of the 42 patients with positive pathologic findings and positive washings, 25 (60 per cent) have died, 14 (33 per cent) are alive with no evidence of disease for 2 to 36 months, and 3 are alive with disease at 15 months, 18 months, and 25 months, respectively.

Of the 114 patients with positive pathologic findings and negative washings, 60 (52.6 per cent) are alive with no evidence of disease for 2 to 36 months, 41 (36.0 per cent) have died, 11 (9.6 per cent) are alive with disease, and 2 have been lost to follow-up study.

Of the 42 patients with negative pathologic findings and positive washings, 33 (79 per cent) are alive with no evidence of disease for 2 to 36 months, 6 have died within 2 years, 2 are alive with disease, and 1 was lost to follow-up.

Of the 204 patients with negative pathologic findings and negative washings, 176 (86.3 per cent) are alive with no evidence of disease for 2 to 34 months.

It should be noted that no claim is made that these figures represent a valid representation of the prognostic significance of peritoneal washings. This is only a preliminary study of the desirability and feasibility of conducting a properly designed co-operative clinical study.

DISCUSSION

The sensitivity of peritoneal washings as an assay technique is not known but could be improved by the development of a practical method for using and completely recovering a large volume of saline and perhaps also by the use of streptolysin O to lyse the red cells and neutrophils. Cytochemical studies and supravital staining have been tried as additional techniques to reduce the number of false diagnoses but are not completely satisfactory.

Undoubtedly some false positive diagnoses will be made, particularly of mesothelial cells, which may be large with an immature appearance, may have a relatively large nucleolus, and may be found in clumps. Their recognition as nonmalignant cells depends upon their uniform appearance without cytoplasmic or nuclear abnormalities. In contrast, most tumor cells may have one or more of the following: relatively large nuclei and nucleoli, pseudopodiumlike projections of the nuclei, bizarre mitotic spindles, polyploidy, and extraordinarily deep staining, indicating excesses of both deoxyribonucleic acid and ribonucleic acid. Tumor cell clumps are more compact and the cell boundaries often overlap, whereas mesothelial cells most often are seen as sheets of cells.

Cell culture has been used to confirm the viability of cancer cells isolated from ascitic fluid. We have cultured peritoneal washings without much success. In contrast to the poor growth of tumor cells in washings, the culture of tumor cells from established ascitic fluid with large tumor cell populations is almost always successful. The previous adaptation of these cells to growth in a fluid medium is probably advantageous.

These studies clearly indicate that the exfoliation of tumor cells into the peritoneal cavity parallels the extent of the tumor growth. As might be expected, the incurable patients had a higher frequency of positive tumor cell washes than the curable ones had. Significant increases in numbers of tumor cells associated with operative manipulation occurred only when the patients had gastric and ovarian carcinoma, but some of the operative procedures in these cases were only palliative.

The prognostic significance of finding isolated tumor cells in the peritoneal cavity cannot be determined at present. It would appear, however, that with at least 1 positive pathologic finding, i.e., metastases, serosal involvement, ascites, or implants, and with tumor cells present in the peritoneum, the prognosis is grim. Of the 42 patients with this combination of findings, 25 (60 per cent) have died in a follow-up ranging up to 36 months, and a number of those alive are still only in their first or second year of follow-up.

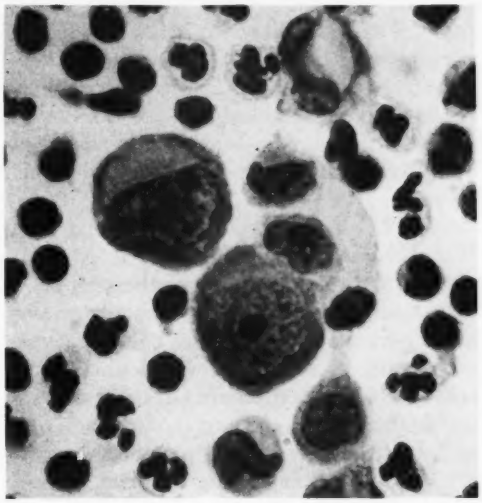


FIG. 3. Tumor cells in washing at the end of gastric resection.

In contrast, among the group of 114 patients with at least 1 positive pathologic finding, but with negative washings, only 40 (35 per cent) are dead in a follow-up ranging up to 36 months. In this group, also, a number of patients are still in their first or second year of follow-up, and it is quite conceivable that the ultimate margin may be somewhat less.

The difficulty in assessing the prognostic value of positive peritoneal washings alone in the face of negative findings in regard to metastases, serosal involvement, ascites, or implants is pointed up in the 42 cases of this type, among which only 6 patients have died so far. This figure may become more significant after a longer follow-up, as a number of patients are still in their first follow-up year.

In our opinion, however, these studies are important because they provide more complete data on tumor cell spread, may indicate the extent of the body's defenses against

unestablished tumor cells as well as which patients are most likely to benefit from local chemotherapy, and aid in subsequent evaluation of chemotherapeutic effectiveness. As mentioned previously, it would seem desirable to initiate a statistically valid cooperative study of this kind of tumor cell spread.

SUMMARY

1. Diagnostic washings of the peritoneal cavity in 727 surgical patients with malignant lesions of the stomach, colon, rectum, ovary, uterus, and cervix were found to contain single neoplastic cells and cell clumps in 235 instances, 32.3 per cent.

2. In 421 cases in which resection was considered to be curative, the number of positive washings was 84 (20.0 per cent).

3. Malignant cells were most frequent in washings from patients with incurable disease, particularly those with peritoneal implants, ascitic fluid, or histologic evidence of serosal invasion.

4. Most false positive diagnoses were the result of confusing atypical mesothelial cells with cancer.

5. Papanicolaou smear preparations were superior to dry smears stained by the Wright-Giemsa method.

6. There was no clear-cut evidence in this study that operative manipulation increased the frequency of positive washes in curable cases.

7. In 42 instances, the washings contained tumor cells even though there was no evidence of spread of disease. Six such patients subsequently died of disease.

8. Peritoneal washings may be an aid in selecting patients for local chemotherapy and in the subsequent evaluation of its effectiveness.

REFERENCES

1. Dahle, T. Transtubal spread of tumor cells in carcinoma of the body of the uterus. Surg. Gyn. Obst., 1956, 103: 332–336.
2. Keettel, W. C., and Elkins, H. B. Experience with radioactive colloidal gold in the treatment of ovarian carcinoma. Am. J. Obst. Gyn., 1956, 71: 553–568.
3. Lücke, A., and Klebs, E. Beitrag zur Ovariotomie und zur Kenntnis der Abdominalgeschwülste. Arch. path. Anat., 1867, 41: 1–15. Cited in Papanicolaou, G. N.: Atlas of Exfoliative Cytology. Cambridge, Mass.: Harvard University Press, 1954.
4. Moore, G. E., and Sako, K. The spread of carcinoma of the colon and rectum; a study of invasion of blood vessels, lymph nodes, and the peritoneum by tumor cells. Dis. Colon Rectum, 1959, 2: 92–97.
5. Moore, G. E., Sandberg, A. A., Burke, E. M., Johnson, R., and Katz, A. D. Tumor cells in the blood and body cavity associated with malignancy of the lung and gastrointestinal tract. Surgical Forum, Clinical Congress, 1957. Vol. VIII, pp. 152–157. Chicago: American College of Surgeons, 1958.
6. Pomeranz, A. A., and Garlock, J. H. Postoperative recurrence of cancer of the colon due to desquamated malignant cells. J. Am. M. Ass., 1955, 158: 1434–1436.
7. Quan, S. H. Cul-de-sac smears for cancer cells. Surgery, 1959, 45: 258–263.
8. Spjut, H. J., Hendrix, V. J., Ramirez, G. A., and Roper, C. L. Carcinoma cells in pleural cavity washings. Cancer, 1958, 11: 1222–1225.

THE VASCULAR PATTERN OF THE GASTRIC MUCOSA OF THE RAT FOLLOWING VAGOTOMY

G. NYLANDER, M.D., and S. OLERUD, M.D., Uppsala, Sweden

OUR RELATIVELY DETAILED knowledge of the vascular topography within the gastric wall is largely the result of the excellent investigations by Barclay, Bentley, Barlow, and others. Historical aspects and earlier literature on this topic have been presented by Barlow, Bentley, and Walder, and recently by Schnitzlein.

According to these investigators, the gastric wall is supplied by vessels branching off from the arterial chains at the lesser and greater curvatures. Perforating the muscular layers unbranched, they ramify into a rich submucosal plexus. From this arterial net, mucosal arteries arise, and, anastomosing partly below partly above the muscularis mucosae, they finally divide into slender arterioles, perpendicularly perforating the mucosal membrane. Between these mucosal arterioles, a very rich capillary network is spun, enclosing the glandular crypts. The venous return is collected from a network at the mucosal surface the meshes of which surround the glandular openings and empty into straight mucosal veins perpendicularly penetrating the mucosal depth. These are drained by submucosal veins corresponding to the arteries of this layer.

Arteriovenous anastomoses were demonstrated in the submucosal layer by Barclay and Bentley using a double injection technique—differently stained substances for arterial and venous vessels, viz., coarse injection material, incapable of entering the capillary area. The arterial part of the shunt was usually a direct branch from a mucosal artery, and the venous a mucosal vein. There was a narrow junctional portion with cells of the "musculo-epitheloid" nature, considered capable of swelling. The existence of an arteriovenous communication was further indicated by oxygen saturation determinations on gastric arterial and venous blood. Its relationship to the autonomic nervous system was shown to be that of closure upon vagal and opening upon sympathetic stimulation, according to these authorities. The capillary unit could thus be bypassed at times of functional rest of the stomach. With functional demands, however, the blood flow was considered to enter the capillary area—a mechanism much like that found by Trueta and colleagues to exist in the kidney.

In examining the regulation of blood flow through the stomach wall of the rat, Schnitzlein estimated the vascular effect of different drugs but also performed vagal and sympathetic stimulation and, furthermore, vagotomy followed up by sympathetic stimulation. The vascular reaction upon vagotomy was, however, not made clear. Besides, no microangiographic examination was carried out.

Considering the developing importance of vagotomy as a method to control unmanageable cases of peptic ulcer, we have found it of interest to examine microangiographically its effect on the vascular and especially capillary bed of the gastric mucosa.

MATERIAL AND METHODS

Sixteen young albino rats of the same strain and weighing 200 to 250 grams were used. In 12 cases vagotomy was performed transperitoneally with open ether anesthesia. The relatively coarse vagal nerves were easy to identify close to the abdominal portion of the esophagus. Vagal resection, 5 millimeters in length, was carried out to-

From the Department of Surgery, University Hospital, Uppsala, Sweden.

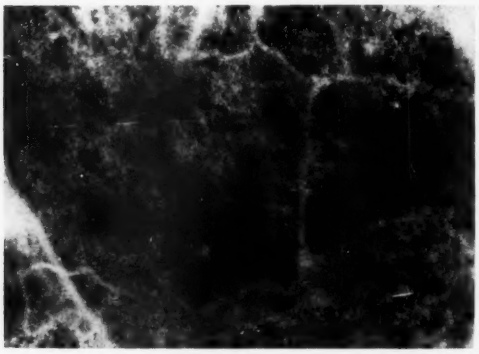


FIG. 1.

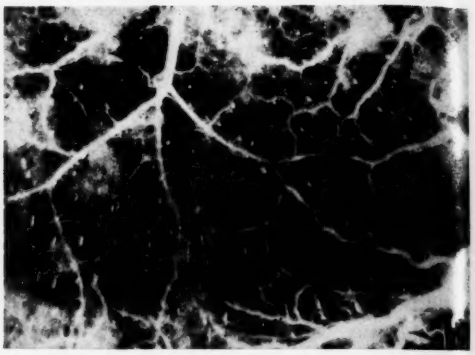


FIG. 2.

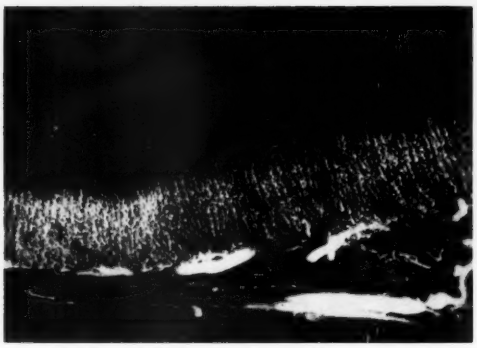


FIG. 3.

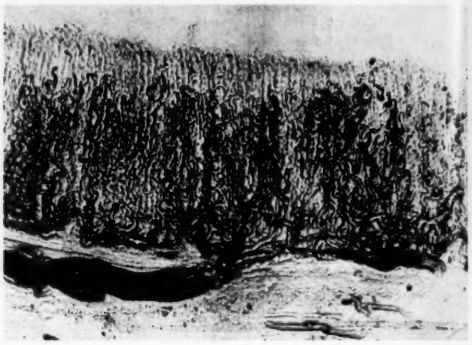


FIG. 4.

FIG. 1. The secretion part of the normal rat stomach immersed in clearing solution; reflected light; black background. Note the heavy cloudiness of the diffuse capillary filling. The deep submucosal vascular plexus is hardly seen.

FIG. 2. The secretory part of the normal rat stomach. Note the clear spots between insular cloudiness of heavy capillary filling. The submucosal vascular plexus is clearly seen as a checkered background.

FIG. 3. Transverse section of the normal gastric wall. Preparation mounted between cover glasses; reflected light. Note the complete filling of mucosal arterioles and capillary area. The coarse submucosal vessels are clearly seen.

FIG. 4. Transverse section of the normal gastric wall; transmitted light; higher magnification. The mucosal arteriolar and capillary systems are completely visualized. A coarse submucosal vein is seen draining some slender, perpendicular mucosal veins.

gether with stripping of the esophageal wall for a distance of 5 to 10 millimeters. Additionally, a pyloroplasty was made.

Four animals were sham-operated upon with open ether anesthesia by performing a laparotomy and handling the esophagus. These animals were used as controls.

The animals were kept for periods varying from 1 to 4 weeks. They all appeared healthy during this time. No significant difference in weight increase was noted between the experimental and control groups.

The animals were ultimately subjected to microangiography. Before this procedure was started, no restrictions in food or water intake were made. The animals were given histamine dihydrochloride subcutaneously and after 5 minutes were anesthetized with open ether. Laparotomy was performed, and a catheter brought down in the stomach, which thus was filled with physiologic saline at a pressure of 10 centimeters of

FIG. 5.

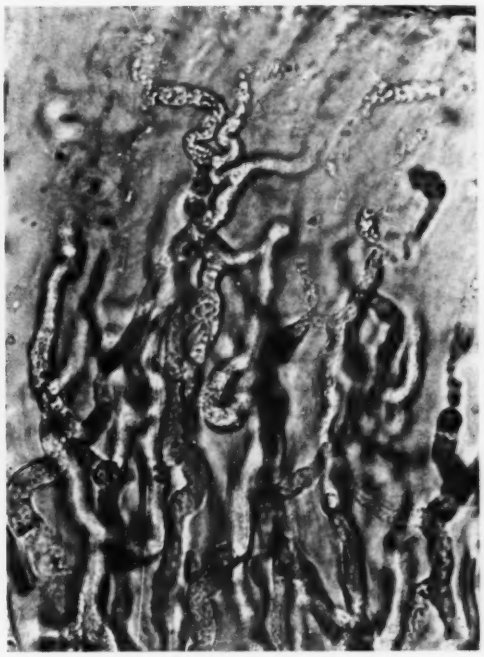


FIG. 6.

FIG. 5. The same picture as in Figure 4. Higher magnification.
FIG. 6. The same part of the gastric mucosa in still higher magnification. Note the benzidine-stained red blood corpuscles and the anastomosing capillary net, spun between the perpendicular mucosal arterioles.

water and a temperature of 38 degrees C. to avoid disturbance in vascular filling by chance caused by different amounts of gastric contents.

The infusion and visualization technique were described in an earlier report (5). The methods include the use of micropaque as contrast substance, benzidine-staining of red blood corpuscles according to the method of Sjöstrand to check the accuracy of the infusion technique, and clearing of the tissues according to Spalteholz. After proper air evacuation, a preliminary examination was carried out stereoscopically using a dissecting microscope. The whole secretory part of the stomach—the investigation was concerned with this gastric portion only—thus immersed in the clearing solution was inspected by reflected light against a dark background. Furthermore, this method enabled us to cut out thin, transverse sections from the preparation under full visual control. These were mounted between cover glasses with a drop of the clearing solution, evacuated of air, and examined in detail microscopically using high enlargements.

OBSERVATIONS

Normal controls. On preliminary inspection, the cleared specimen of the whole gastric secretory portion from an animal subjected to a sham-operation had a very characteristic appearance (Fig. 1). The mucosal surface was completely cloudy in certain areas. The white contrast cloudiness was composed of a delicate, honeycomb-like pattern of small round meshes. These were the capillary loops encircling the glandular crypts. By microscopic dissection through the depth of the preparation, the

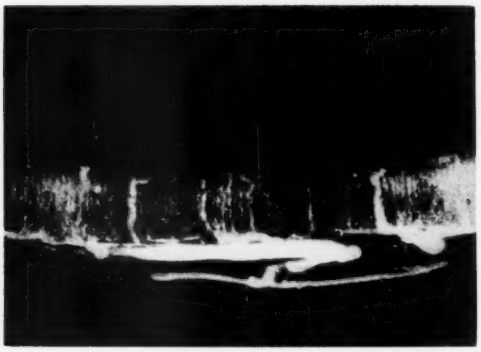


FIG. 7.

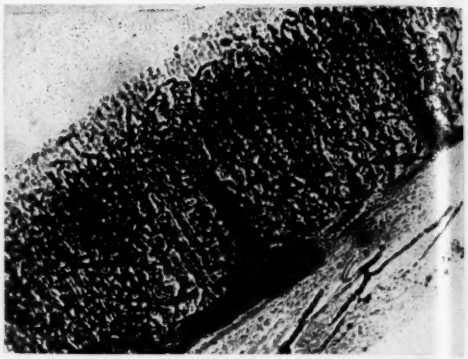


FIG. 8.

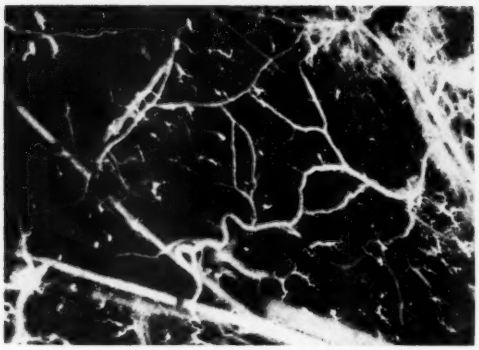


FIG. 9.

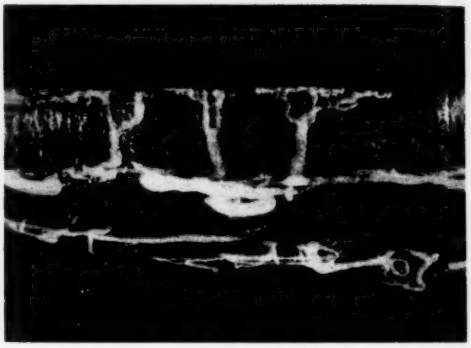


FIG. 10.

FIG. 7. Preparation dissected out from a "clear spot" in the normal stomach; transverse section; mounting that of Figure 4; rather coarse, perpendicular mucosal veins draining into submucosal veins. The arteriolar and capillary filling is in places fairly rich; reflected light.

FIG. 8. The same preparation as in Figure 7. Note the rich arteriolar and capillary filling. The coarse perpendicular vein is well demonstrated; transmitted light.

FIG. 9. The secretory part of the vagotomy animal. Practically no capillary filling is noted. The preparation is free from cloudiness. Its dominating feature is the starfish formations of collecting mucosal veins. The submucosal, vascular plexus is clearly seen.

FIG. 10. Transverse section of the gastric wall in vagotomy; reflected light. Note the very coarse tree-like perpendicular mucosal veins, draining a rich venous system at the mucosal surface and emptying into submucosal veins. The arteriolar and capillary filling is very sparse.

heavy capillary filling could be seen throughout the mucosal layer. The richly anastomosing submucosal vessels formed a checkered background to the capillary pattern mentioned. In other parts of the gastric secretory area, however, another vascular picture was met with. Here, the capillary pattern of a honeycomb was found in circumscribed areas only. Between these, small clear spaces were seen with sparser capillary pattern. In these spaces, centrally located, rather coarse contrast-filled vessels appeared which were shown to be collecting mucosal veins (Fig. 2).

Upon detailed examination of mounted specimens, it was found that in transverse sections cut out from an area with diffuse capillary filling (Fig. 3), the slender mucosal arterioles completely filled the mucosal layer (Figs. 4 and 5). Between the arterioles, the interlacing capillary network was spun (Figs. 5 and 6). In this dense vascular pattern it was very difficult to distinguish any veins, but here and there, a

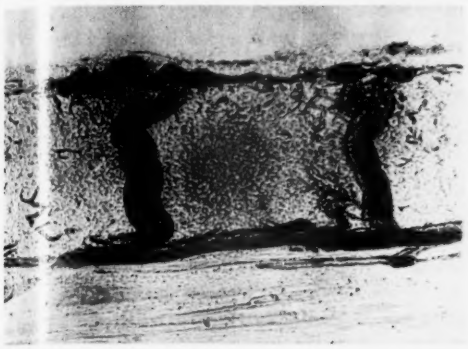


FIG. 11.

FIG. 11. The same preparation as in Figure 10. Higher magnification; transmitted light. Here the mucosal collecting veins are clearly demonstrated as well as the anastomosing venous net at the mucosal surface. Note the mucosal arterioles, emptying into the venous plexus at the mucosal surface.

FIG. 12. The corkscrew-like, mucosal arterioles are seen to empty into the surface veins. No capillary structures are seen.

collecting submucosal vein was observed to drain some rather delicate perpendicular mucosal veins (Fig. 4).

In the areas of spotty, sparce capillary filling and with central, coarse vessel formations, the transverse sections accordingly showed spaces with fewer mucosal arterioles and corresponding capillary network. Instead, the coarse mucosal veins stood forward draining the anastomosing venous meshes on the mucosal surface (Fig. 7). Immediately limiting such an area, a very dense pattern of mucosal arterioles with anastomosing capillary loops was always found (Fig. 8). Thus, arteriolar and capillary filling could be rather dense even around coarse, perpendicular mucosal veins.

Vagotomized animals. Upon preliminary inspection of the whole gastric portion, the secretory part of the stomach showed a vascular architecture quite different from that of the normal controls. Few, if any areas of cloudy, capillary filling could be seen. Instead, coarse vascular formations shaped like starfish were spread throughout the surface of the preparation (Fig. 9). The significance of these was shown to be that of mucosal collecting veins around the glan-

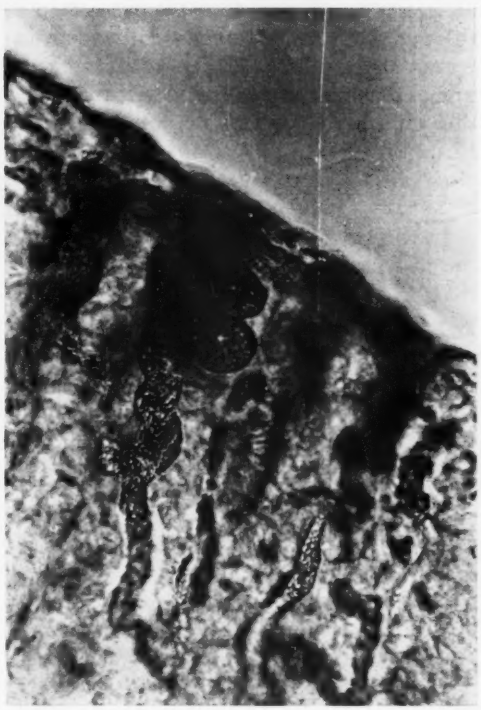


FIG. 12.

dular openings continuing into corresponding perpendicular mucosal vein stems. On account of the very sparse arteriolar filling, the preparation was strikingly translucent, and the checkered pattern of submucosal vessels was clearly seen.

Upon detailed examination of mounted specimens, it was found that thin, transverse sections from these preparations clearly demonstrated the very coarse, perpendicularly running mucosal veins (Fig. 10), draining a heavy, anastomosing venous network at the mucosal surface. As suggested by the preliminary inspection, few mucosal arterioles were seen and capillary units were only occasionally observed (Fig. 11). In higher magnification, the characteristic mucosal veins were strikingly outlined, ornamentally penetrating the mucosal layer from surface to bottom and collecting into submucosal vein stems. Further, it was clearly demonstrated that coiling mucosal

arterioles emptied into the venous system at the mucosal surface directly without an intervening capillary net. The occurrence of mucosal arteriovenous communications was thus established, as may be noted in Figure 12.

DISCUSSION

In the normal rat given histamine before the microangiographic procedure, the vascular response of the gastric mucosa often was that of a diffuse filling of the mucosal arterioles and corresponding capillary net. Furthermore, earlier observations on the circulatory unit of the gastric mucosa, referred to in the introduction, were confirmed in detail.

The vascular reaction mentioned was not always uniform. Insular parts of the gastric mucosa developed somewhat less pronounced arteriolar and capillary filling. In these spaces, centrally located, perpendicular, mucosal veins dominated the picture. It was thus seen that only rarely, even with histamine stimulation, the whole gastric mucosa developed full arteriolar and capillary filling. Areas of circulatory and consequently functional rest in a relative sense could thus be demonstrated. The significance of this arrangement might best be illustrated by the findings in the vagotomy group.

Here, the arteriolar and capillary filling was extremely sparse throughout. The coarse mucosal veins collecting the anastomosing venous system at the mucosal surface were most prominent. Of utmost interest were the sparse, coiling arterioles seen to emerge directly into the venous loops at the mucosal surface. We are of the opinion that these obvious, arteriovenous communications are to be considered as part of the arteriovenous shunting system of the gastric wall, earlier believed to exist in the submucosal layer only. As mostly no capillary units were open there is no other way for the infused contrast substance to reach the collecting veins but through the arterioles, ascending through the mucosal layer.

SUMMARY

1. Vagotomy was performed on a series of white laboratory rats and the secretory part of the stomach investigated microangiographically. Controls were sham-operated on.

2. Histamine dihydrochloride was given prior to the microangiographic procedure.

3. The vascular response of the normal gastric mucosa—secretory part—was of dense filling of arterioles and capillary net.

4. Certain insular spaces were found to be in relative circulatory rest with fewer arterioles and capillary units filled. Large, collecting, mucosal veins dominated such spaces emptying into submucosal vein stems.

5. In the vagotomized animals the arteriolar filling was very sparse throughout. The vascular pattern was characterized by the very coarse, perpendicular mucosal veins, draining the anastomosing venous plexus at the mucosal surface. Sparse mucosal arterioles were seen to empty into the aforementioned venous net forming arteriovenous communications.

6. The opinion is expressed that these are part of the arteriovenous shunting system of the gastric wall, earlier considered to exist only in the submucosal layer.

REFERENCES

1. Barclay, A. E. Micro-arteriography. Brit. J. Radiol., 1947, 20: 394.
2. Barclay, A. E., and Bentley, F. H. Vascularisation of human stomach. Gastroenterology, 1949, 12: 177.
3. Barlow, T. E. Vascular patterns in the alimentary canal. Visceral Circulation. A Ciba Foundation Symposium, p. 21. London: J. & A. Churchill Ltd., 1952.
4. Barlow, T. E., Bentley, F. H., and Walder, D. N. Arteries, veins and arteriovenous anastomoses in the human stomach. Surg. Gyn. Obst., 1951, 93: 657.
5. Nylander, G., and Olerud, S. A simple microangiographic procedure for study of the vascular pattern in the alimentary canal. Acta Soc. med. Upsal., 1960, 65: 374.
6. Schnitzlein, H. N. Regulation of blood flow through the stomach of the rat. Anat. Rec., 1957, 127: 735.
7. Sjöstrand, T. Eine Methode fuer quantitative Bestimmung der Blutmenge in den feineren Blutgefaessen in verschiedenen Organen und in verschiedenen Geweben desselben Organen. Skand. Arch. Physiol., Berlin and Leipzig, 1934, 68: 160.
8. Spalteholz, W. Ueber das Durchsichtigmachen von menschlichen und tierischen Praeparaten. Leipzig, 1914.
9. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L. Studies on the Renal Circulation. Oxford: Blackwell Scientific Publications Ltd., 1947.

CLINICAL AND CINERADIOGRAPHIC EVALUATION OF THE MATHISEN URETEROSIGMOIDOSTOMY

JOHN McL. MORRIS, M.D., F.A.C.S., New Haven, Connecticut, and
KRISTAPS J. KEGGI, M.D., New York, New York

PERMANENT URINARY DIVERSION remains a surgical problem, as is indicated by the number and variety of solutions that have been put forward. Recently the trend has swung toward the use of the ileal conduit described by Bricker and advocated by Cordonnier, Stamey and Scott, and others. This procedure has the distinct advantages of isolation from the fecal stream, elimination of back pressure from the bowel, and rapid transit of urine resulting in decreased electrolyte reabsorption. It has the disadvantages of requiring an additional abdominal stoma and of the complications arising from the two extra small bowel suture lines.

An ingenious technique for urinary diversion was described by Mathisen in 1953. In studying the cloacae of birds, in which the urine empties directly into the rectum, he observed that there were small ureteral nipples, somewhat similar to the papilla of Vater. He concluded that this arrangement might prevent reflux and devised a technique for the surgical construction of such a nipple (Figs. 1 and 2). It is our purpose to evaluate a series of cases in which this technique was employed.

CLINICAL MATERIAL

Forty procedures involving urinary diversion into the bowel were performed at Yale-New Haven Medical Center between September 1953 and January 1959. These included 22 Mathisen ureterosigmoidostomies, 15 Bricker ileal conduits, and 3 miscellaneous procedures.

From the Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven. This investigation was supported in part by research grant No. C-2536 from the National Institutes of Health, U. S. Public Health Service.

Analysis was undertaken of the patients with the Mathisen ureterosigmoidostomies. Of the 22 patients in this series, 13 were alive in September 1960, representing 2 to 7 year survivals. The total number of renal units implanted into the sigmoid with the Mathisen nipple was 41. That there are only 41 renal units instead of the logical 44 is explained by the fact that 2 patients had unilateral ureteroenterostomies and 1 patient had a mucosa-to-mucosa anastomosis on one side because of a short ureteral segment and a Mathisen nipple on the other.

Primary diagnoses. The primary diagnoses leading to urinary diversion in patients with Mathisen ureterosigmoidostomies included 16 cases of carcinoma of the cervix, 3 of carcinoma of the bladder, 2 of extrophy, and 1 of corpus carcinoma.

Operative complications and mortality. The immediate postoperative course of this group of patients was as follows: uncomplicated, 13; fever of undetermined origin, 3; thrombophlebitis, 2; sigmoidal fistula, 2; ileus, 1; atelectasis, 1; ileal perineal prolapse, 1; and death from pneumonia, 1.

A palliative urinary diversion performed on an anuric patient with a nonprotein nitrogen level of 156 resulted in death on the third postoperative day from a massive Pseudomonas aeruginosa pneumonia. This represents the sole operative death, a 4.5 per cent mortality.

There were 2 sigmoidal fistulas, apparently at the site of the bowel closure over the nipple. In one of these the nipple could be visualized and was intact. The patient died in a few months of extensive recurrence. The second fistula closed spontaneously.

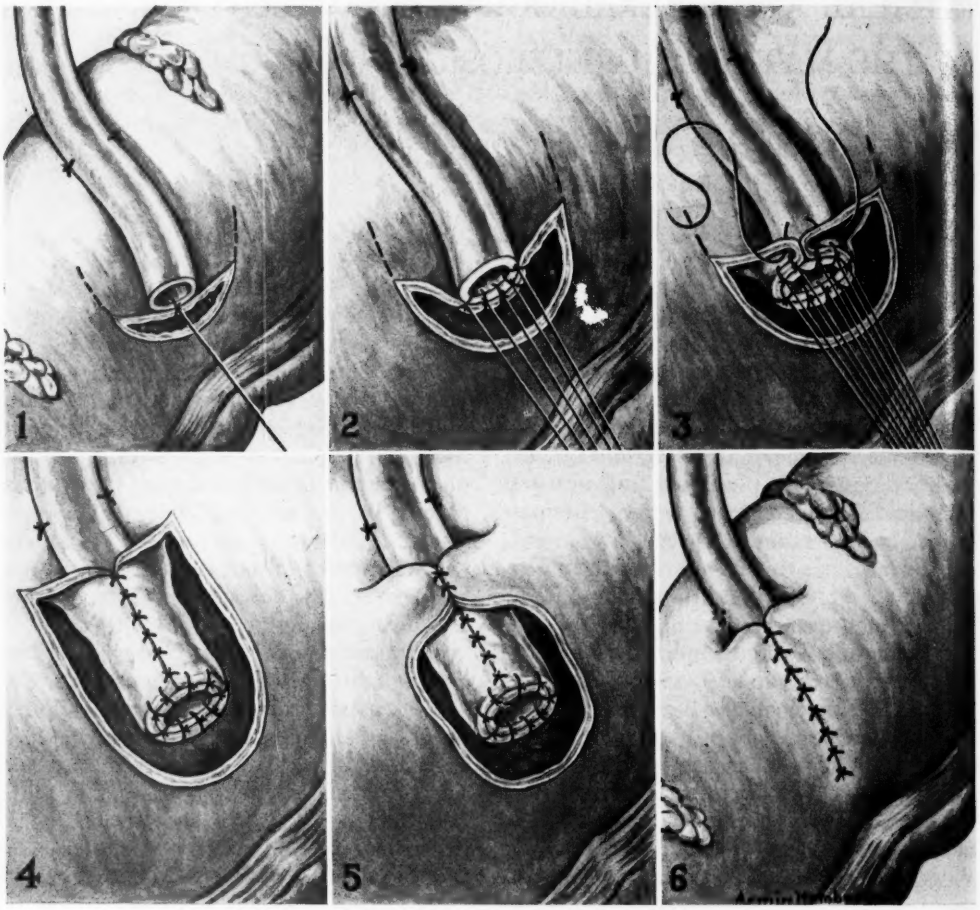


FIG. 1. Sketch showing method of ureterointestinal anastomosis. The nipple, constructed with reversed full thickness bowel on the outside, is approximately 2 centimeters in length. Bowel closure over the nipple is done in two layers. (Modified after Mathisen, 8).

Postoperative hospitalization varied from 8 to 43 days with an average of 20 days.

EVALUATION OF RENAL STATUS

Pyelonephritis. The exact incidence of pyelonephritis after surgery of this nature is difficult to determine accurately. Insofar as possible, symptoms were elicited by direct questioning for history of flank pain or unexplained fever.

With the exception of 1 patient who had definite bouts of pyelonephritis due to a fragment of catheter in the right ureter and who was anuric at time of admission, there were no cases of pyelonephritis requiring hospitalization.

After discharge from the hospital 3 patients experienced mild episodes suggesting possible pyelonephritis. On one occasion 6 years postoperatively 1 patient had a temperature of 100 degrees F. with slight costovertebral angle tenderness; a second patient complained of occasional fever and backache but was never seen with these symptoms; a third patient had 1 episode of mild pyelonephritis during the first 6 month

period. It is of interest that studies showed ureteral reflux in all 3 of these patients.

Nonprotein nitrogen levels. The extent of renal obstruction and damage prior to surgery in some instances is reflected in the fact that 5 patients were uremic with preoperative nonprotein nitrogen values of 58, 77, 126, 137, and 156 milligrams per 100 cubic centimeters, respectively. Although elevated values tended to fall after surgery, in 8 patients there was an immediate significant postoperative rise in nonprotein nitrogen levels which warrants explanation. The indwelling ureteral catheters advocated by Mathisen were not used for a number of reasons, chief of which was the questionable advisability of having a tube permitting infection to ascend from the bowel lumen into the renal pelvis. On the other hand, the edema about the nipple in the early postoperative phase in some cases resulted in little if any urinary output for the first few days and produced a rather marked postoperative rise in the nonprotein nitrogen level which subsided before discharge. This appeared to have no permanent effect as far as could be determined.

Two patients who had a normal nonprotein nitrogen value at the time of hospital discharge, had long term elevations—1 of 50 milligrams per 100 cubic centimeters at 5½ years, and 1 of 55 milligrams per 100 cubic centimeters at 3½ years. In both of these patients anterior exenterations were performed, and both showed ureteral reflux on the cineradiograms to be discussed.

Intravenous pyelography. As a means of facilitating the study of renal status, pyelographic changes have been classified in a 0 to 4 range which is similar to that used by Bricker in his follow-up studies:

	No. of renal units	
	Preoperative	*Follow-up*
Grade 0—normal kidney	19	15
Grade 1—minimal hydronephrosis	6	9
Grade 2—moderate hydronephrosis	5	6
Grade 3—massive hydronephrosis	6	2
Grade 4—nonvisualization (nonfunction)	5	2

With our technique, progression in hydronephrosis occurred not infrequently in the immediate postoperative period of 2 to 4 weeks. Twelve of 24 renal units studied (50 per cent) showed some increase, as contrasted with only 4 showing immediate decrease. This tendency could be explained in terms of postoperative edema at the site of the anastomosis. This assumption seems to be further confirmed by the fact that 11 of 19 renal units showed decrease in hydronephrosis during the period between the postoperative and follow-up intravenous pyelograms taken at 2 months and 6 plus years, suggesting that the edema had subsided and released temporary obstruction.

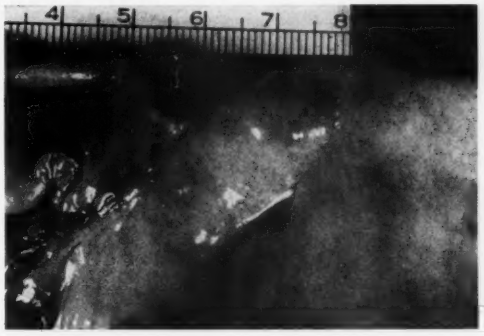


FIG. 2. Appearance of nipple from within the lumen of the bowel on the third day. This specimen is from the only patient in this series who died postoperatively.

The pattern of increase in hydronephrosis during the postoperative period and decrease at follow-up is shown in Figures 3, 4, and 5 with a progression from a normal left kidney preoperatively, to moderate hydronephrosis postoperatively, and then a return to normal on the 3 year follow-up film. The nonfunctioning right kidney has recovered satisfactorily.

Evaluation of the over-all change from the time of the preoperative intravenous pyelogram to follow-up shows that of 29 renal units studied 15 units had no change in renal status, as demonstrated by intravenous pyelogram, and that 6 units showed decrease in hydronephrosis. The 8 remaining units available for follow-up study which showed increase in hydronephrosis are of more concern.

FIG. 3. Preoperative intravenous pyelogram showing normal left kidney and nonfunction on the right.

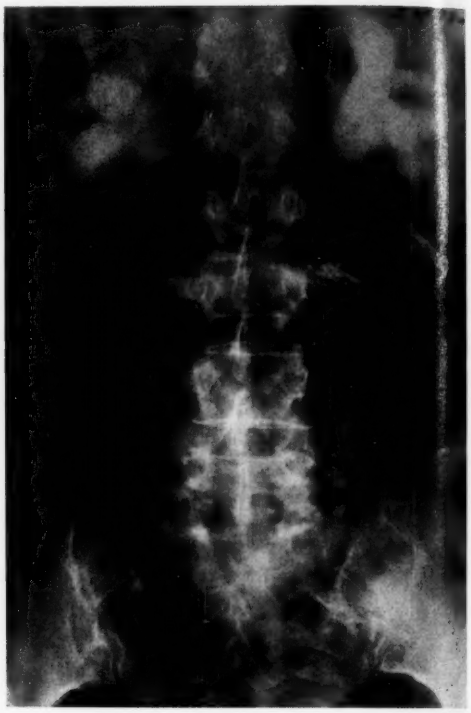


FIG. 4. Pyelogram taken 3 weeks postoperatively showing grade 2 hydronephrosis bilaterally.

The most probable causes for increasing hydronephrosis would appear to be obstruction from recurrent disease, stricture from the anastomosis, or a nonfunctioning nipple valve with transmission of intracolonic pressure to the ureter and renal pelvis. Although in this small group there is not enough information to permit definite conclusions, in 3 units rapid recurrence of the disease makes neoplastic obstruction likely. In 3 other units without known recurrence, 1 with exstrophy, stricture seems probable. In the remaining 2 units the demonstration of ready reflux through the nipple rules out any acceptable explanation on the basis of obstruction and indicates that high intracolonic pressure transmitted to the renal pelvis, with accompanying infection, is probably responsible.

Electrolyte disturbances. Hyperchloremia with hypokalemia is considered to be the main electrolyte disturbance associated with ureterosigmoidostomy. During the postoperative hospital course 4 of 22 patients had a temporary elevation of chloride to 112, 112, 113, and 118 milliequivalents per liter, respectively. In association with the occurrence of the hyperchloremia in this last patient there was a hypokalemia which was transient and has not been apparent on follow-up study.

At follow-up, hyperchloremia was detected in 2 patients only. One patient showed an elevation of chloride to 115 milliequivalents per liter without other electrolyte abnormalities 4 months postoperatively, which subsequently returned to normal. Another patient had an elevation of chloride to 114 to 123 milliequivalents per liter, a serum carbon dioxide content of

14.7 to 19.7 milliequivalents per liter, normal sodium and potassium levels, but a nonprotein nitrogen value of 50 to 55 milligrams per 100 cubic centimeters 6 years postoperatively. This patient had an anterior exenteration and showed ureteral reflux on other studies.

CINERADIOGRAPHIC STUDIES ON URETERAL REFLUX AND THE EFFECT OF INTRACOLONIC PRESSURE ON THE KIDNEY

Studies by Berglin and Mathisen have shown intrapelvic pressures in the kidney to be considerably lower than the intraluminal pressures encountered in the colon. Renal intrapelvic pressures of 7 to 10 millimeters of mercury could be increased somewhat by coughing or straining, but at 45 millimeters of mercury urine secretion ceased. Resting intracolonic pressures of 5 to 30 millimeters of mercury would rise during defecation to 80 millimeters of mercury. Colonic pressures of 150 to 180 millimeters of mercury produced by straining have been recorded. Although such high pressures are transient, the objective of this surgical approach has been to create a workable valve preventing not only the free movement of contaminants from the colon into the ureter and kidney but also the direct transmission of these pressures to the renal pelvis.

In order to evaluate the effect of increased intracolonic pressures cineradiographic techniques were employed to record ureteral and renal pelvic peristalsis and to note ureteral reflux of barium. The cineradiographic examinations were made with a Phillips image intensifier and a 16 millimeter Auricon camera equipped with a sound track. The intracolonic pressures were determined by means of a large Foley catheter introduced into the rectum or colostomy and connected to a water manometer. These pressures were recorded vocally on the sound track of the cineradiographic film, thus obtaining a concurrent record of the visible fluoroscopic changes and the bowel pressures.

Ureterorenal peristaltic activity in 7 renal units was observed by this technique. In this limited series of cases intracolonic pressures as high as 94 centimeters of water had no visible effect on the peristalsis of the renal collecting system or ureters. The peristaltic waves appeared to pass along normally and empty into the bowel in the face of the elevated pressures, although unfortunately these observations cannot be reproduced in still photographs.

FIG. 5. Pyelogram taken 3 years postoperatively showing normal left kidney and grade I hydronephrosis on the right.

A second step in the study was to determine ureteral reflux of barium with the colon filled with barium under gradually increasing pressures. Reflux of barium from the colon into the ureters was found in 3 of 15 renal units studied (Figs. 6 and 7). In 1 case the barium outlined the renal pelvis (Fig. 8). Although in some instances there was no reflux with intracolonic pressures as high as 90 centimeters of water, it is of note

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 6. Cineradiographic view showing reflux of barium up the right ureter at a pressure of 36 centimeters of water.

FIG. 7. Cineradiographic view showing reflux of barium up left ureter at a pressure of 42 centimeters of water.

FIG. 8. Cineradiographic view of barium in left renal calyces at a pressure of 42 centimeters of water. The study was made 5 years postoperatively.

that the reflux that did occur occurred at the relatively low pressures of 36 to 42 centimeters. Reflux at low pressures means that the patient can and probably does have reflux of fecal material during the activities of a normal day.

This is borne out by the fact that all 3 patients showing barium reflux on cineradiography had spontaneous air reflux on routine intravenous urography. All roentgenograms and intravenous urograms of the patients with Mathisen anastomoses were carefully examined for evidence of air reflux. It was found that pneumoureters were evident in 5 of 32 renal units thus evaluated, or 15.6 per cent. It is of note that in 4 of these 5 renal units pneumoureters were evident on repeated examinations which tends to indicate a constant defect permitting a reflux of air from the colon and free movements of contaminants.

Whether reflux occurred in spite of the nipple or whether in the cases of reflux the construction of the nipple had failed it is not possible to say. It was found in some instances, in which progression of the underlying disease permitted pathologic examination, that a nipple had completely flattened out, losing any possibility of valve action. With cineradiography the ureteral nipples in some cases appeared to be outlined in the films. In others they could not be made out. In those with reflux, however, it was not possible to be sure one way or the other.

DISCUSSION

The ultimate success or failure of any urinary diversion procedure is measured on the basis of its clinical results. The evaluation of the patient's clinical status in many instances is difficult because the underlying process requiring surgery is of a serious nature and is frequently fatally progressive.

Results will obviously be better if one is operating on young patients with congenital defects or on patients with relatively early untreated cancers than if one is undertaking the operation as a last resort in advanced cases of gynecologic malignant disease in which radiation therapy has failed. Because of the mutilating nature of exenterative surgery, it has been our policy to avoid such procedures when there is any other form of therapy available. Cases of malignant disease, therefore, all represented radiation therapy failures and far advanced disease.

We have found the Mathisen ureterosigmoidostomy to be more satisfactory than some of the earlier methods of ureterosigmoidostomy. In this small series, complications appeared to be somewhat fewer than reported after the techniques evaluated by Creevy, Ferris and Jacobs and their associates, and Lapides. Except for the postoperative complications listed and deaths from disease, the only serious problems noted on clinical follow-up examination appeared to be of renal origin.

Cineradiographic studies have proved of help in evaluating the function of the ureteral nipple. In a small number of cases ureteral reflux was demonstrated. Such reflux appeared to occur at relatively low intracolonic pressures. It is, of course, possible that the nipples were improperly constructed, but there was concern about the possibility of stricture if they were constructed too snugly.

The exact significance of ureteral reflux is not clear. In this series, however, the 3 patients who had a history of possible late pyelonephritis and 2 with long term nonprotein nitrogen elevations showed ureteral reflux, suggesting that such reflux has a very unfavorable influence.

The observation of ureteral reflux in a small number of cases should not be taken as an indictment of the Mathisen procedure. It has certain definite advantages and has proved very satisfactory on the whole. Cineradiographic studies have not been carried out extensively on other types of ureterointestinal anastomoses and might yield useful information.

SUMMARY

In our hands the Mathisen ureterosigmoidostomy has proved a satisfactory technique of urinary diversion, with no more complications than reported after other methods. Cineradiographic studies suggest that, with adequate valve action at the nipple, increased colonic pressure does not appear to affect ureteral peristalsis. In a small number of cases ureteral reflux was demonstrated in spite of the construction of a nipple. Such reflux appears to occur at relatively low intracolonic pressures and appears to be associated with a higher incidence of late renal damage.

REFERENCES

1. Berglin, T., and Mathisen, W. Electrolyte imbalance following ureterointestinal anastomosis. Acta chir. scand., 1952, 104: 130.
2. Bricker, E. M., Butcher, H. R., and McAfee, C. A. Results of pelvic exenteration. Arch. Surg., 1956, 73: 661.
3. Cordonnier, J. J. Ileal bladder substitution; an analysis of 78 cases. J. Urol., Balt., 1957, 77: 714.
4. Creevy, C. D. Facts about ureterosigmoidostomy. J. Am. M. Ass., 1953, 151: 120.
5. Ferris, D. O., and Odel, H. M. Electrolyte pattern of the blood after bilateral ureterosigmoidostomy. J. Am. M. Ass., 1950, 142: 634.
6. Jacobs, A., and Sterling, W. B. Late results of ureterocolic anastomosis. Brit. J. Urol., 1952, 24: 259.
7. Lapides, J. Mechanism of electrolyte imbalance following ureterosigmoid transplant. Surg. Gyn. Obst., 1951, 93: 691.
8. Mathisen, W. A new method for ureterointestinal anastomosis. Surg. Gyn. Obst., 1953, 96: 255.
9. Stamey, T. A., and Scott, W. W. Ureteroileal anastomosis. Surg. Gyn. Obst., 1957, 104: 11.

BLOOD PRESSURE AND OSMOLARITY CHANGES IN THE DUMPING SYNDROME

RAYMOND C. READ, M.D., F.R.C.S., and DON SWENSEN, M.D., Minneapolis, Minnesota

VASOMOTOR PHENOMENA of flushing, sweating, and palpitation with a sensation of heat or cold frequently accompany the dumping syndrome. These signs and symptoms have been attributed to activation of the sympathetic nervous system in response to the oligemia which arises from osmotic withdrawal of fluid into the bowel. However, elevated skin temperatures, increased digital blood flow, and renal hyperemia are not the usual sequelae of a reduction in circulating blood volume. The present investigation was undertaken to provide further information regarding this paradox. The blood pressure response to a standard hyperosmotic meal was studied before and after gastric surgery in patients suffering from duodenal ulcer. Individuals who were known to have the disorder were investigated similarly. Measurements of plasma osmolarity were carried out concurrently as it has been demonstrated recently that hypertonicity itself can initiate vascular effects.

METHODS

All of the patients who were investigated had been referred for surgical treatment of peptic diathesis. Measurements were carried out with the subjects in a fasting state and while in the supine position. This position was used because of easy reproducibility and also because its reported therapeutic value would presumably increase the significance of any data obtained.

In a typical experiment, the blood pressure was monitored at 2 minute intervals using a standard sphygmomanometer cuff with an automatic recorder. After a steady state had been reached, 150 to 200 milliliters of 0.9 per cent saline were given orally and observations were continued during the next 30 to 60 minutes. The procedure was then repeated using a similar volume of 50 per cent glucose. A few determinations were carried out during and after meals or phlebotomy. The maximal pulse pressures recorded before and after exposure to the various tests were abstracted as indices of the patients' response. Mean pressure was calculated empirically as diastolic pressure plus one-third the pulse pressure. Venous blood samples were drawn at 10 minute intervals throughout the studies and their freezing points determined with a Fiske osmometer.

RESULTS

A total of 45 blood pressure tracings were obtained in 26 patients. Three of these from 2 patients have been excluded because the pressures at rest were greater than 150/100. The results for the remainder have been divided into four groups—patients with duodenal ulcer, those with dumping syndrome, effect of phlebotomy, and changes in plasma osmolarity. These data are reported in millimeters of mercury.

Patients with duodenal ulcer. A consecutive series of 10 men was studied immediately prior to operation and the results are summarized in Figure 1. Control pressures were within the normal range and remained so after the patients drank the isotonic and hypertonic solutions. Pulse pressures averaged 33 initially, 34 after saline, and 38 with glucose; none experienced symptoms.

Six of the 10 patients were reinvestigated 4 to 11 days postoperatively. All but 1 patient had had a 75 per cent gastric re-

From the Surgical Department, Veterans Administration Hospital, and the University of Minnesota, Minneapolis.
This work was supported by U. S. Public Health Service Grant No. H-4287 and the Minnesota Heart Association.

section. Reconstruction of the gastrointestinal tract was carried out by performing a gastrojejunostomy in 4 and a gastroantrostomy in 1 patient. In the remaining individual, vagotomy and pyloroplasty were performed. Control pressures were similar to those recorded preoperatively and again remained unaltered by the ingestion of 0.9 per cent saline (Fig. 1). However, although mean pressures were unchanged by 50 per cent glucose, the systolic rose and the diastolic fell in each instance (Fig. 2). Thus, the most significant alteration was in the pulse pressure which, after glucose, reached an average of 59 compared to the previous value of 32. Whereas symptoms were not evoked by saline, 5 of the 7 complained of either sweating, fullness, abdominal cramps, flushing, nausea, or vertigo after the administration of glucose. One of the 2 asymptomatic individuals had had both vagotomy and pyloroplasty; his pulse pressure increased 43 per cent with glucose. The other had undergone a Billroth II gastrectomy and there was a somewhat greater increase of pulse pressure, from 25 to 40.

The 6 patients who underwent gastrectomy were re-evaluated 10 to 12 months later, and the findings did not differ significantly from those obtained previously (Fig. 3). Pulse pressures increased from 33 to 53 with glucose, and 5 patients again experienced symptoms. Questioning of these individuals revealed that they had all complained occasionally after meals. None was incapacitated.

Patients with dumping syndrome. Eleven patients who continued to have noticeable postcibal symptoms for some years after gastric surgery were investigated next. Control pressures were again found to be within normal limits and remained so in the 10 patients who were tested with isotonic saline (Fig. 4). Fifty per cent glucose produced marked changes. The average blood pressure went from 111/75 to 135/64, thus doubling the pulse pressure from 36 to 71. Typical dumping episodes ensued in 9 out of 10 patients. Two of the group were also

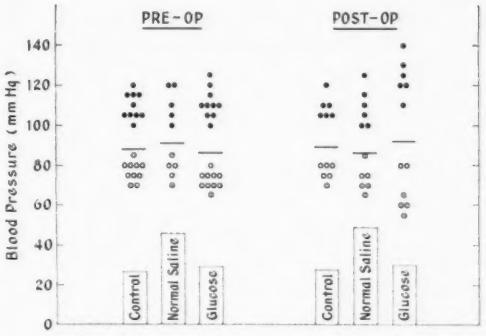


FIG. 1. Maximal systolic, diastolic, and over-all mean pressures registered in patients with duodenal ulcer before and after ingestion of 200 milliliters of 0.9 per cent saline or 50 per cent glucose. Preoperative readings were obtained the day prior to surgery and postoperative values, in 6 of the 10, 11 to 14 days later. All measurements were made with the patient in the supine position while in a fasting state. The solid dots represent systolic values, open circles diastolic, average calculated means indicated by the horizontal lines throughout.

studied while eating breakfast. While reclining they were fed by an attendant to avoid any artefact which might result from muscular exercise. The typical blood pressure response (Fig. 5) was observed in association with complaints of sweating, nausea, flatulence, and abdominal cramps.

Effect of phlebotomy. Five blood pressure studies were made during and after phle-

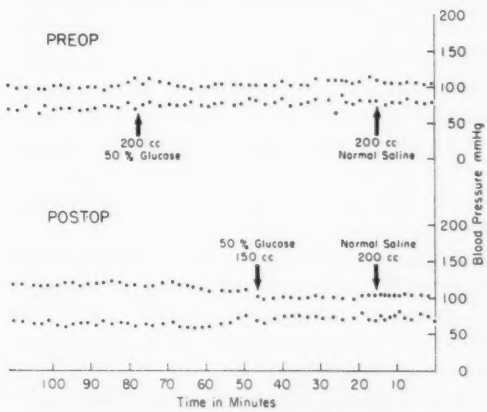


FIG. 2. Reproduction of a representative original recording taken from 1 of the patients represented in Figure 1. Note the significant change is a widening of the pulse pressure seen only postoperatively and then with administration of glucose but not with saline.

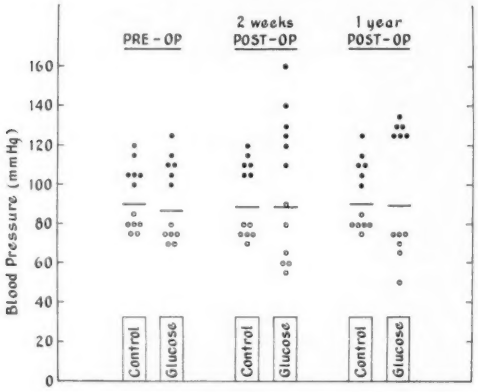


FIG. 3.

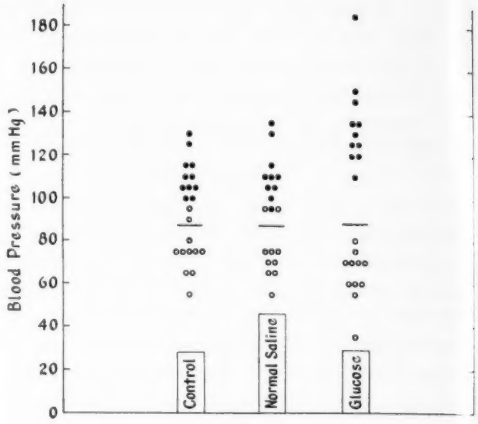


FIG. 4.

FIG. 3. Maximal blood pressure recordings before and after the administration of 50 per cent glucose to 6 patients with duodenal ulcer before, immediately after, and 1 year subsequent to gastrectomy. Note that despite the increases in pulse pressure registered postoperatively the mean pressure remains remarkably constant.

FIG. 4. Blood pressure responses of 11 patients with dumping syndrome to isotonic saline and 50 per cent glucose.

FIG. 5. Blood pressure record from a patient known to have dumping syndrome who was fed breakfast while reclining in bed.

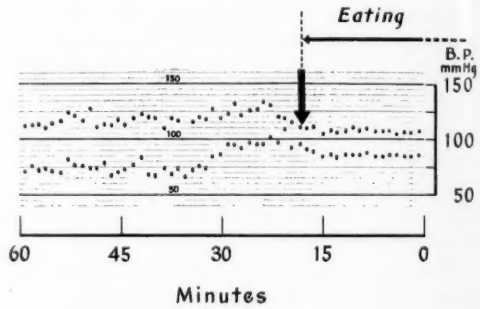


FIG. 5.

botomy. Three patients with dumping syndromes from the previous group were bled 500 milliliters in 4, 4, and 5 minutes respectively. Blood pressure in every instance remained unaffected (Fig. 6), and there were no complaints. Similarly, widening of the pulse pressure did not occur in 2 normal donors (Fig. 6) as a result of hemorrhage.

Changes in plasma osmolarity. Osmometric determinations were performed on 8 of the duodenal ulcer patients before and after operation. Preoperatively, plasma osmolarity was unaffected by the ingestion of hyperosmolar glucose solutions. Postoperatively, a consistent transitory blood hypertonicity developed after 50 per cent glucose was given (Fig. 7). The average increase was from 5 to 10 milliosmols per liter.

DISCUSSION

Opinion is divided in the literature on the question of whether the blood pressure rises or falls during episodes of dumping. Earlier writers, influenced by Hoffman's concept of blood being diverted into the visceral circulation in response to a meal, considered hypotension to be the rule. However, in 1945, Custer, Butt, and Waugh observed systolic hypertension and for this reason excluded shock as a causal mechanism in the disorder. Their findings were confirmed by both Machella and Fisher and associates. Meurling reported that the blood pressure did not change except in association with severe symptoms; it, then, frequently rose but occasionally fell. Duthie and associates agreed. In 1955, Roberts and her co-workers described an almost uniform decrease dur-

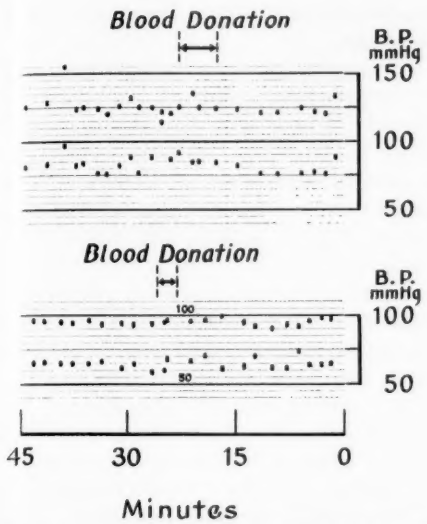


FIG. 6. Graph shows that hemorrhage failed to affect the blood pressure in a patient with dumping syndrome, above, and in a normal individual, below.

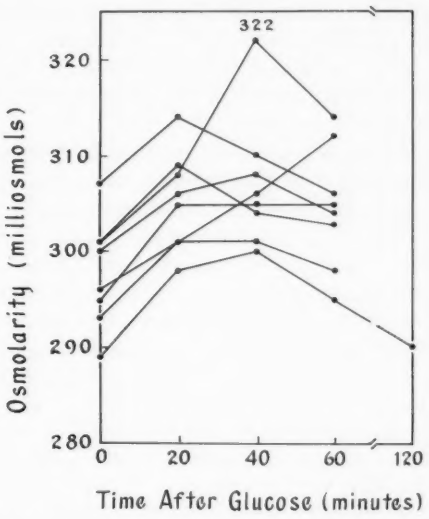


FIG. 7. Consistent rise and fall in plasma osmolarities after 150 to 200 milliliters of glucose given orally. Measurements made in postoperative duodenal ulcer patients.

ing dumping. Pontes and Neves presented similar data. The present studies show that although the mean pressure remains remarkably constant, homeostasis is only maintained by a significant increase in pulse pressure. The consistency with which this vasomotor alteration can be demonstrated probably depends upon strict control of posture and minimal interference with the patient while measurements are being made.

Widening of the pulse pressure in the absence of marked bradycardia or an appreciable rise in cardiac output, neither of which occurs in the dumping syndrome, indicates either an increase in the elastic coefficient of the vascular bed or an accelerated run off through the capillary bed. The former possibility seems improbable and, thus, a state of lowered peripheral resistance or vasodilatation would appear to accompany the other aspects of the dumping syndrome. Hinshaw and his associates arrived at a similar conclusion on the basis of blood flow determinations. They concluded that patients with dumping syndrome react abnormally to oligemia by dilation rather than constriction of the peripheral vasculature. The hemorrhage experiments do not support such an explanation but provide instead further support for those who have recently questioned the prime role of oligemia in the pathogenesis of the syndrome. Some of the original proponents of the blood volume depletion theory now believe that the amount of fluid abstracted osmotically into the intestine is inadequate to explain all of the findings. A shift of 5 to 10 per cent of the water out of red cells and plasma with intravascular pooling appears to be more important. It is of interest that this order of magnitude determined experimentally in the dog is similar to the change in osmolarity which has been found postoperatively in man. This increase in blood tonicity is presumably related to rapid absorption of digestive products with movement of water in a reverse direction. Hypertonicity of this degree evokes vasodilatation as well as widespread activation of cholinergically innervated effector cells. Interestingly enough, the blood pressure changes and symptomatology observed in connection with the dumping syndrome bear a striking resemblance to those described after the admin-

istration of acetylcholine or acetyl-beta-methylcholine. A similar picture is produced by the widespread enhancement of tissue acetylcholine activity with di-isopropyl-fluorophosphate.

The foregoing considerations lead to the hypothesis that although the dumping syndrome, like syncope, simulates a state of shock with associated sympathoadrenal release, it actually represents a manifestation of cholinergic-like activity brought about by transient hyperosmolarity. The bowel is affected primarily, but the cardiovascular system and other parts of the body may also become involved if the osmotic stimulus is transferred rapidly to the blood stream. Under normal conditions, this process is prevented by the ability of the stomach to protect against the passage of hyperosmolar content into the bowel as demonstrated by the unchanged plasma osmolarities recorded preoperatively. This function is easily disrupted by operation or intubation and then complaints can be provoked experimentally in the majority of patients by the ingestion of hypertonic solutions. In those in whom symptoms could not be elicited the usual blood pressure changes still appeared. Previous investigators have commented upon a similar disparity between signs and symptoms. It would seem possible, therefore, that certain patients may continue unaware of the underlying physiologic disturbance the tendency to which from the present observations seem to persist for a considerable time after operation.

SUMMARY

The blood pressure response to the oral administration of isotonic and hypertonic solutions was measured before and after operation for duodenal ulcer. Similar determinations were carried out in patients with dumping syndrome. A few readings were obtained after meals or phlebotomy. The effect of these procedures on the osmotic pressure of the blood was also investigated.

The results show that 0.9 per cent saline is without effect upon the blood pressure. However, 50 per cent glucose, after but not before gastrectomy, induces a significant increase in pulse pressure. This vasodilatory reaction still occurred 1 year after surgery. The response in patients with dumping syndrome was similar to but greater than that in unselected postgastrectomy patients and could be evoked by meals. Pulse pressure changes were not observed after hemorrhage. There appeared to be a relationship between the blood pressure alterations and an increase in plasma osmolarity.

These findings suggest that the dumping syndrome represents a manifestation of the body's response to hyperosmolarity. While the reaction occurs primarily in the gut, the cardiovascular system and other parts of the body become involved by transfer of the stimulus through the intestinal wall.

REFERENCES

1. Custer, M. D., Butt, H. R., and Waugh, J. M. The so-called dumping syndrome after subtotal gastrectomy. Ann. Surg., 1946, 123: 410–418.
2. Duthie, H. L., Irvine, W. T., and Kerr, J. W. Cardiovascular changes in the postgastrectomy syndrome. Brit. J. Surg., 1959, 46: 350–357.
3. Fisher, J. A., Taylor, W., and Cannon, J. A. The dumping syndrome; correlations between its experimental production and clinical incidence. Surg. Gyn. Obst., 1955, 100: 559–565.
4. Hinshaw, D. B., Jorgenson, E. J., Davis, H. A., and Stafford, C. E. Peripheral blood flow and blood volume studies in the dumping syndrome. Arch. Surg., 1957, 74: 686.
5. Hoffman, V. Die kleine Magenresektion (nack Reichel) Beim Ulcus Duodeni und Ventriculi in dem Ergebnis Meiner Nachuntersuchungen. Arch. klin. Chir., 1939, 195: 312–341.
6. Machella, T. E. The mechanism of the postgastrectomy "dumping" syndrome. Ann. Surg., 1949, 130: 145–159.
7. Meurling, S. Postcibal symptoms after partial gastrectomy for peptic ulcer. Acta Soc. med. Upsaliensis 1953 (Supp. 3), 1: 127.
8. Pontes, J. F., and Neves, D. P. Adrenal stimulation in the dumping syndrome. Gastroenterology, 1953, 23: 431.
9. Roberts, K. E., Randall, H. T., Bane, H. N., Medwid, A., and Schwartz, M. K. Studies of the physiology of the dumping syndrome. N. York M. J., 1955, 55: 2897–2902.

EDITORIALS

SUPPURATIVE PAROTITIS

LOUIS T. BYARS, M.D., F.A.C.S., St. Louis, Missouri

PRESIDENT GARFIELD was struck by an assassin's bullet on 2 July 1881. He died on 19 September after an illness marked by constant infection, the loss of 85 pounds in weight, and severe suppurative parotitis which was drained surgically, but not adequately. Mathew Brady, the noted photographer of Civil War battlefield scenes, died in 1896 of nephritis and suppurative parotitis. This complication occurred most often in critically ill patients and, thus, was an omen of dire import.

Now, since the early 1940's, several generations of surgeons have come into being and have conducted busy practices blissfully unaware of this complication which their predecessors had cause to fear. Medical writers moved on to more pressing problems. When the subject was mentioned it was to repeat beliefs fashionable in the 1930's which had not been subjected to critical evaluation. Principles of treatment of "surgical mumps" were altogether forgotten.

It was but natural that the controlled roentgen ray, 35 years old in 1930 and still mysterious, should be tried empirically in the treatment of troublesome conditions such as parotitis. As this particular therapy became popular, the seriousness and, strangely, even the incidence of parotitis seemed to decrease. At this same time, a better understanding of the needs of the depleted human body was developing rapidly. Hydration of the patient, maintenance of electrolyte balance, and blood replacement were practiced with increasing efficiency. Because of better diagnosis, surgical resections of the intestinal tract for cancer were performed prior to the onset of obstruction or extreme debilitation.

The diminishing problem of suppurative parotitis vanished after the advent of the sulfonamides and antibiotics. Radiation therapy for this condition remained unchallenged in the literature. An article was published entitled, "Suppurative Parotitis; a Vanishing Disease."

The circle is complete and suppurative parotitis is again being found as a serious complication in some surgical patients. Even the young and vigorous individual may be afflicted. The resistant staphylococcus is involved.

The treatment of the acute condition which is progressing is early surgical drainage for the relief of pain, identification of the causative organism, and prevention of the necrosis of tissue and sepsis which occur when an infection progresses within an organ encased in a relatively unyielding capsule.

Reliance upon radiation therapy in such a case is not warranted.

It is uncommon, indeed, to find an article which bridges a 20 year gap in the surgical literature as well as does the one on acute pyogenic parotitis by Spratt.

THE SCRUB NURSE—A VANISHING SPECIES

GEZA DE TAKATS, M.D., F.A.C.S., Chicago, Illinois

THE QUICK-WITTED, dexterous, devoted instrument nurse, who after 20 years of service was still paid the salary of a recent graduate on floor duty, who knew and cherished every instrument in the set and took tremendous pride in her job, is disappearing. The tower of strength in propulsive hemorrhage, the wise critic of attending and house staff is on her way out. The remaining ones are visible in the teams headed by chiefs of surgical services who may thus not always be aware of the trials and tribulations of the rank and file working in a pandemonium which deserves a brief description.

The scene is at 1 p.m. in a general hospital. The surgeon who could not get any operating room space in the morning has gulped down 2 cups of cold, bitter coffee and is waiting for the morning crew to vacate the room. When he finally enters the scene an hour late, he finds a circulating nurse showing the instruments to a recent graduate who has only scrubbed twice before. There are 3 student nurses standing around as observers, a nurse's aid whose aseptic conscience has not yet been developed, and a number of nondescript floating personnel who are scrubbed, capped, and masked for "on the spot" training.

The exploration of the common duct proceeds slowly. The surgeon is aware of this, since at another teaching institution he would now be halfway through. By 3 o'clock, the nursing staff shows signs of visible and audible restlessness. The changing of the guard is about to take place, some of whom may never show up, but the characters who now appear defy description and may be a subject of another communication. With much moving about, stirring up air currents, bacteria, and overhead lights, the new shift has taken charge.

The circulating nurse is a grandmother who now helps out her alma mater. The instrument nurse likes the afternoon shift because she can sleep late in the morning. She is quite bright and has two interns in tow, one of whom might take her back to South America where, she gathers, one has a lot of servants. She has not the slightest interest in surgical procedures or in her role as part of the team. She is well aware of the vast shortage of nurses and knows that the Chief has indoctrinated his staff to be lenient and understanding with the operating room personnel—"otherwise we will have nobody!"

The operation proceeds slowly with occasional interruptions because of lack of certain instruments, even although the surgeon is an accomplished technician. It terminates with one sponge missing, to be found after a long search, in a bucket, discarded by one of the "on the spot" trainees, saddled by this time with an instructor.

Only if one is blind or living in an ivory tower can he call this brief sketch exaggerated or an attempt to be funny. It was only used to illustrate a growing disruption of the surgical teamwork, to trace the causes of this development, and to suggest improvement.

Obviously, the number of operating rooms, the number of operations, and the more intensive use of operating room space are steadily increasing. Operations today are far more extensive and demand far more nursing care, preoperatively, during operations, and postoperatively. There is an easily documented shortage of nursing care, and progressive directors of nursing can readily supply extensive data regarding ratio of population to nursing and the distribution of nurses in the administrative, supervisory, and educational fields—anything but nursing care.

The bright, alert, and ambitious group of instrument nurses is gradually being withdrawn from the operating table to circulate, to supervise, to instruct. They are urged to take a B.S. in nursing and more recently, a doctorate. Thus, with a few notable exceptions, only the untrained, the immature, and the transient remain for the job which requires manual dexterity, concentration, and daily growing experience.

It is to the everlasting credit of the nursing profession that it recognized a national need and began to train—without much help from the administration or the surgical

profession—a group of surgical technicians. These were pioneer individual efforts, which culminated in an *Instructor's Manual of Surgical Technical Aides*, issued by the American Hospital Association in 1954. The manual was designed as a guide toward the training of surgical technical aides, a rather tortured description of an operating room technician, to be taught preferably by a full time professional nurse, over a period of 200 hours. This was the first attempt to standardize a number of individual efforts undertaken by operating room supervisors who were aware of the growing lack of skilled instrument nurses.

From the standpoint of the surgeon, leading a team of assistants, technicians, and trainees and "consulting" with the anesthetist, it is a superior advantage to have a skilled professional worker, who has stature, rising salary, and adequate pension, to facilitate a technical procedure. This job is purely technical, has no relation to nursing care, and consequently needs no nurse's education. The "comprehensive nursing care" that the nursing educators are so concerned about is safeguarded by the circulating nurse whose many responsibilities now include the instruction and supervision of the technician.

It is a curious fact, however, that, while most surgeons returning from World War II busied themselves with setting up recovery rooms and intensive therapy wings, so little was done about continuing their experience in civilian hospitals with the superior help they obtained in the Armed Services. A notable exception was that of Hedley Atkins who addressed the British Ministry of Health on 29 March 1949 advocating the training of first-class operating room technicians under less than a year and divorcing this training entirely from the nursing career. He likened this group to physical therapy or radiology technicians.

Many of us have ignored or have been unaware of the development of this technical group; it has been relegated to a "nurse's aid" category, not endangering the professional and economic status of the professional nurse and constituting sound administrative practice to the hospital administrator.

The surgical profession ought to take a good look at this problem. Why can't we standardize, nay elevate, the standards of such technical training by establishing a proper and desirable teamwork. Certainly the nursing profession has taken a far-reaching step by creating these jobs. A nursing director knows only too well that about 10 per cent of her nursing power is in the operating room and that there are consistent and insistent demands for actual patient care, not to speak of the ever increasing force of instructors, undoubtedly the superior material.

The training of technicians at present seems to consist of courses, varying from 1 month to a year, carried out by individual institutions of varied aims and capacities. In many instances, this training is far more intensive and prolonged than that of the student nurse or recent graduate. But in other instances, their training is woefully inadequate, throwing a great burden on the surgeon, on the circulating nurse, and last, but not least, on the patient.

The procurement and standardized training of operating room technicians ought to start in the high schools as a vocational training course similar to that of the practical nurse. Many of these young people may want to go on to study biology or medicine. Unless scholarships become available for everyone who wants to study medicine without having to hold down two additional jobs at the same time, there will be plenty of young people who will take this trade course if properly explained and organized. Hospitals will still have to orient and adapt them to their specific needs. Surgery in the animal hospital could expose medical students, student nurses, and technicians to surgical teamwork. Such a technician, duly licensed and provided with a certificate, should look forward to a dignified, secure status. There should be a carefully deter-

mined ratio between registered nurse and technician; but the help of such "specialists" in the operating room is highly desirable and long overdue in many of our institutions.

In this age of automation, with computers spewing forth diagnostic slips on the basis of ill-observed data, with toll roads effacing the village green and the old fishing pond, we might as well have a well instructed, well paid instrument engineer feed us the proper tools with the proper speed and at the proper time. Aseptic conscience, aseptic feel, knowledge of instruments, and manual dexterity will have to be taught, much of it by audiovisual means.

Right in front of our eyes, there occurs a steady, continuous drainage of instrument nurses into other fields. Since this process is hardly reversible, nay inevitable, it is high time that surgical departments take an active hand in the training and elevating of this type of service. Continuity on the job will require adequate financial compensation but should restore the vanishing teamwork to its previous excellence.

THE SURGEON AT WORK

INTRAHEPATIC ARTERIOVENOUS FISTULA OF HEPATIC ARTERY AND PORTAL VEIN

HARRIS B SHUMACKER, JR., M.D., F.A.C.S., and JOHN A. WALDHAUSEN, M.D.,
Indianapolis, Indiana

COMMUNICATIONS between systemic and pulmonary arteries and veins have frequently been reported and their hemodynamic characteristics well studied. However, fistulas between the hepatic artery and the portal veins are quite uncommon, and only recently have they been recognized clinically and treated with success. For this reason we have thought it advisable to describe a patient with a hepatic artery-portal vein fistula whom we have recently studied.

CLINICAL SUMMARY

The patient was a 41 year old white female who was referred for treatment because of a possible aneurysm of the hepatic artery. The patient stated that she had been well until 7 weeks prior to admission when, after an episode of bronchopneumonia, she had the acute onset of bilateral chest pain associated with cough and fever. The pain localized in the right upper quadrant and the patient entered a local hospital for what was thought to be acute cholecystitis.

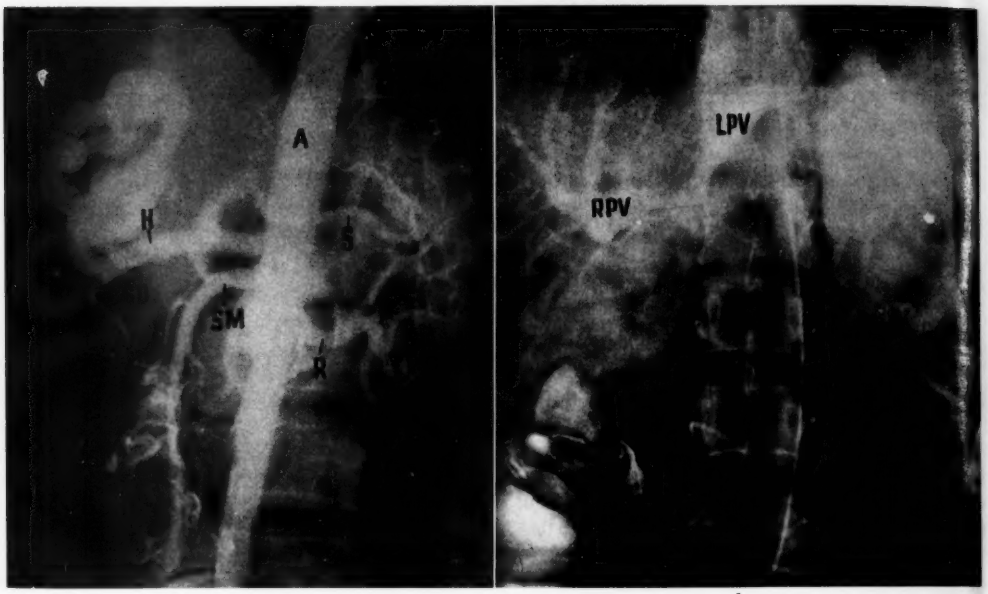
At the time of the emergency laparotomy the gallbladder was thin walled, dilated, and tense with edema of the wall. The hepatic artery lay anterior to both the common duct and the portal vein and was greatly dilated. A cholecystectomy was performed. Examination of the gallbladder showed moderate fibrous thickening of the wall. The serosa was injected. No stones were present. On microscopic examination the gallbladder wall showed some fibrosis and round cell infiltration.

The patient's postoperative course was uncomplicated until 9 days prior to admission when she had a recurrence of her abdominal symptoms. She was then referred to this hospital for treatment. Further questioning revealed that she had lost 20 pounds in the past 2 months. She denied hematemesis, melena, or jaundice. Physical examination revealed a well developed, thin, chronically ill-appearing woman. There was no evidence of jaundice. The blood pressure was 90/20 millimeters of mercury, the pulse 84 beats per minute, and the temperature 98.6 degrees F. Abnormal findings were confined to the abdomen. There was a well healed recent right paramedian incision. A pulsatile mass measuring about 4 centimeters in diameter was felt just to the right of the umbilicus. Auscultation revealed a continuous murmur over the lower part of the chest wall, especially on the right, and the upper portion of the abdomen. Results of laboratory studies including hemoglobin, hematocrit, white blood cell count, urinalysis, fasting blood sugar, and blood urea nitrogen were within normal limits. Roentgenographic studies of the chest and gastrointestinal tract revealed no significant abnormality except for some diverticula in the sigmoid colon. An electrocardiogram showed occasional premature ventricular contractions. A diagnosis of arteriovenous fistula was made.

An aortogram was made by introducing a catheter percutaneously by the Seldinger technique into the right femoral artery and advancing it to the level of the celiac axis. Thirty milliliters of 90 per cent hypaque were injected (Fig. 1a). The hepatic artery and its left branch were enlarged and tortuous. The left hepatic branch extended into the liver, ending in an area of cavernous dilatation. Subsequent films showed rapid filling of the portal venous system (Fig. 1b). The patient tolerated the procedure well.

Operation was carried out on 6 May. The right lobe of the liver appeared and felt normal. The left lobe pulsated abnormally and here a continuous thrill could be felt. The hepatic artery measured approximately 8 millimeters in outside diameter and divided proximal to both lobes. Thus it was easy to isolate the left hepatic artery. The gastroduodenal artery arose from the left hepatic artery which also gave off a branch to the caudate lobe. The left hepatic artery was transected distal to its extrahepatic branches. The portal vein was easily dissected and its extrahepatic branches were identified. The left hepatic branch was

From the Department of Surgery, Indiana University Medical Center, Indianapolis.
Aided by a grant from the Indiana Heart Foundation.



a b

FIG. 1. a, Preoperative aortogram; Right posterior oblique view. The hepatic artery and its left branch are enlarged and tortuous. The left hepatic branch extends into the liver, ending in an area of cavernous dilatation. b, Subsequent anteroposterior view showing rapid filling of the portal venous system. The nephrogram shows a double kidney on the left side. *A*, Aorta; *H*, hepatic, *GD*, gastroduodenal, *R*, renal, *S*, splenic, and *SM*, superior mesenteric arteries. *LVP* and *RVP*, left and right portal veins.

divided. The left lobe of the liver was then amputated and the capsule closed after the left hepatic duct was isolated and ligated. Once the left lobe was amputated, no thrill was felt.

After operation, the patient did well. She had a transient rise of indirect bilirubin to 1.34 milligrams per cent but this rise subsided to a normal level by the fourth day after surgery. The continuous murmur could not be heard, but to rule out any further arteriovenous malformation a second aortogram was made. At this time the celiac axis and its branches filled well, as did the right hepatic artery. No evidence of an arteriovenous communication could be seen (Fig. 2). Again the patient tolerated the procedure well and was discharged to her home. She has remained well.

PATHOLOGIC EXAMINATION

The left lobe of the liver weighed 180 grams. At the porta hepatis there was a vascular malformation consisting of a large blood vessel with a roughened wall. The vessel was 2 centimeters in circumference. A communication between it and a venous channel was identified where it entered the liver (Fig. 3). The remainder of the vascular supply of the lobe was composed of large and small vascular channels lined by smooth endothelium. The liver parenchyma appeared normal. Microscopic examination showed a normal liver capsule and the usual lobular parenchyma. There were very large vessels with fibrous thickening of the intima (Fig. 4a). The usual vessels were observed in the portal triads (Fig. 4b) but, in addition, there were numerous thin-walled vascular channels without a muscular wall lined by a single layer of endothelium.

DISCUSSION

Fistulas between the hepatic artery and portal vein have only recently been recognized, although Sachs clearly described a fistula between an aneurysm of the hepatic artery and a hepatic vein as early as 1892. Strickler and associates and Madding and his associates reported patients with a hepatic artery-portal vein fistula. They did not hear a murmur. Both patients expired as the result of hemorrhage from esophageal varices. Wheeler and Warren described a patient who bled from duodenal

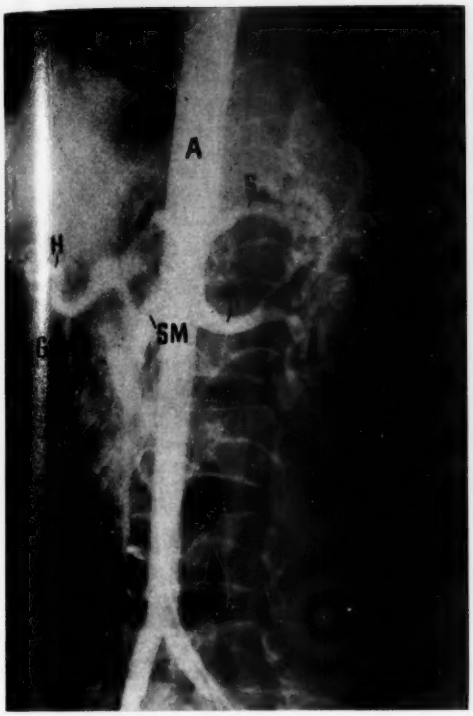


FIG. 2.

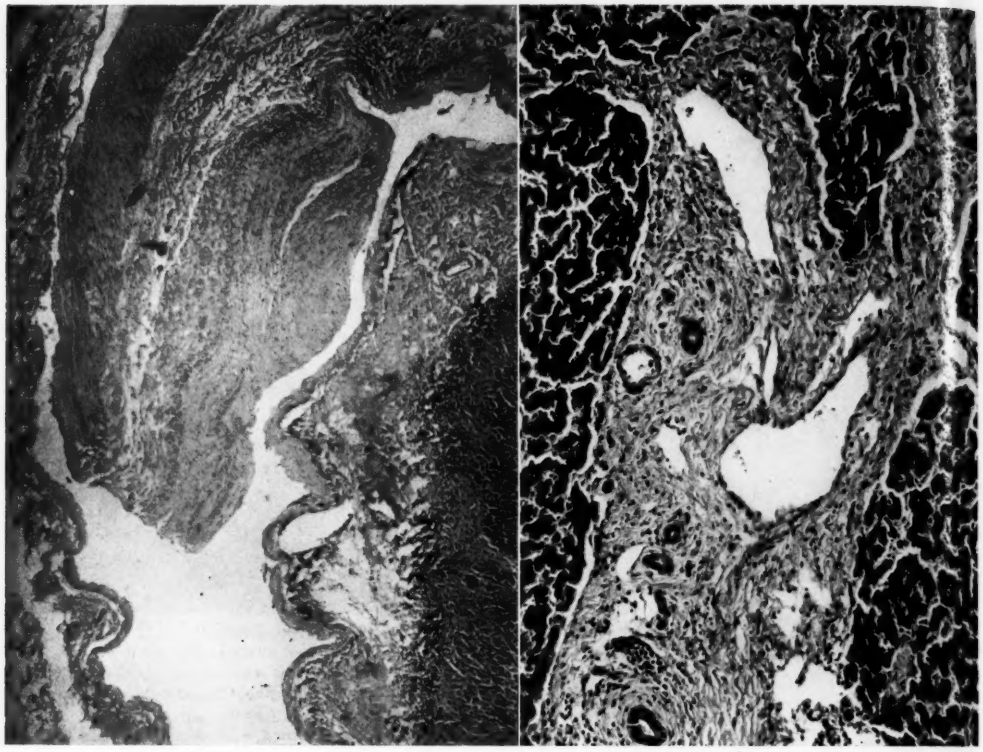
FIG. 2. Postoperative aortogram; anteroposterior view. The celiac axis and its branches fill well, as does the right hepatic artery. There is no evidence of an abnormal arteriovenous communication. The same symbols are used as in Figure 1.

FIG. 3.

FIG. 3. Gross specimen. The communication between the enlarged left hepatic artery, *A*, and the venous channel, *V*, is shown.

varices. He had a splenorenal shunt for portal hypertension, after which a continuous murmur was heard. An aortogram showed a hepatic artery aneurysm with a fistula into the portal vein. The patient was treated by wiring the aneurysm and partially suturing the fistula through the portal vein. He survived. Grant and associates studied a patient who had sustained a hepatic artery-portal vein fistula in addition to an aortic-inferior caval fistula from a gunshot wound. This patient had marked portal hypertension which returned to normal after the fistula was sutured through the vein. This patient also survived. Recently Cohen and DeBakey have reported a patient who also sustained fistulas from a gunshot injury between the hepatic artery and the portal vein as well as between the right renal artery and the inferior vena cava. This patient had a continuous murmur over the abdomen, and the diagnosis was established by aortography. Closure of the fistulas and restoration of vascular continuity were successful.

This lesion experimentally has been of interest to both physiologists and surgeons. Narath (4, 5) attempted to arterialize the portal blood by implantation of either the hepatic artery or the renal artery into the portal vein to prevent necrosis of the liver after ligation of the hepatic artery. Although his efforts were not totally successful, he was convinced that arterialization would allow the liver to survive. Schilling and his associates (7,8) successfully established hepatic artery-portal vein fistulas in dogs. Immediate studies on their animals showed no significant changes in the liver, although the procedure did protect against the anoxic effects of simple ligation of the hepatic artery. However, the animals ultimately showed severe changes in their liver function tests and died. In contrast to the situation in some of the patients presented in clinical reports, portal hyper-



a b

FIG. 4. a, Microscopic section showing the larger artery with fibrous thickening of the intima communicating with a venous channel. b, Microscopic section of the portal triads showing in addition to the usual vessels numerous thin-walled vascular channels.

tension and its sequelae did not appear to be a significant finding. Another difference between the experimental animal and man appears to be the absence of cirrhosis in the latter. Portal hypertension seems to be mainly the result of an increased flow rather than of the increased resistance seen in cirrhosis. Cardiac failure such as occurs with systemic arteriovenous fistulas does not appear to be an important factor in this lesion, probably because the liver capillary bed remains interposed between the arterial tree and the right side of the heart.

The cause of these communications is often obscure, as was true in the case reported here. However, fistulas caused by a ruptured hepatic artery aneurysm or by trauma have been reported. In view of the absence of any other apparent cause and the presence of numerous vascular channels within the portal triads in this patient, the presence of a congenital anomaly seems likely.

The patient presented here differs significantly from those previously reported cases in that she had no evidence of portal hypertension. Although there was no visible or palpable evidence of portal hypertension observed at the time of operation, the portal pressure unfortunately was not measured. The history of acute pain is difficult to explain and it would appear that hematemesis is in general a much more common symptom. On pathologic examination two forms of the lesion are encountered. The patient described in this report had an intrahepatic lesion confined to one lobe. The patients described by Strickler, Madding, and their associates and Cohen and DeBakey had extrahepatic fistulas as did Wheeler and Warren's patients. In the latter report the patient had an

aneurysm of the hepatic artery that had ruptured into the portal vein. Cirrhosis of the liver is not a predominant picture in these patients, although often esophageal varices are present.

The diagnosis should be suspected in any patient with upper gastrointestinal hemorrhage and an associated continuous murmur over the abdomen. Such a murmur unfortunately has not very commonly been reported. It was heard in the patient reported here and in the one reported by Wheeler and Warren, although the murmur was heard in the latter patient only after a splenorenal shunt had been performed for what was originally thought to be portal hypertension caused by cirrhosis. The best conclusive finding is the demonstration of the fistula by aortography. In this patient, and those of Wheeler and Warren and Cohen and DeBakey, the diagnosis was established by injection of radiopaque contrast medium into the aorta at the level of the celiac axis.

The intrahepatic lesion confined to one lobe can be treated by hepatic lobectomy. The loss of a lobe is usually well tolerated, and patients with previously adequate liver function rarely show any evidence of insufficiency. Closure of the fistula by direct suture remains the procedure of choice but is possible only in the extrahepatic lesions. Wheeler and Grant and their associates sutured the communication by approaching it through an incision in the portal vein. Cohen and DeBakey were able to isolate the involved vessels, divide the fistula, and suture the communication.

SUMMARY

The case of a patient in whom a fistula between the hepatic artery and the portal vein was demonstrated by aortography is reported. The abnormal communication was confined to the left lobe of the liver, and successful treatment was carried out by its resection. As far as can be ascertained, this is the first patient successfully treated for intrahepatic fistula between the hepatic artery and the portal vein.

REFERENCES

1. COHEN, A., and DEBAKEY, M. E. A report on the successful repair of traumatic arteriovenous fistulas between hepatic artery and portal vein and right renal artery and inferior vena cava. Surgery, 1960, 48: 548.
2. GRANT, R. N., GLIEDMAN, M. L., and DETERLING, R. A., JR. Co-existing traumatic arteriovenous fistulae between the aorta and vena cava, and the hepatic artery and portal vein complicated by a "Goldblatt" kidney. Ann. Surg., 1958, 148: 286.
3. MADDING, G. F., SMITH, W. L., and HERSHBERGER, L. R. Hepatoportal arteriovenous fistula. J. Am. M. Ass., 1954, 156: 593.
4. NARATH, A. The arteriovenous anastomosis of the portal vein as means of treating necrosis of the liver after ligation of the hepatic artery. Zbl. Chir., 1915, 42: 1.
5. Idem. The origin of anemic necrosis of the liver after ligation of the hepatic artery and its cure by arterio-portal anastomosis. Deut. Zschr. Chir., 1916, 135: 305.
6. SACHS, R. Zur Casuistik der Gefusserkrankungen. Deut. med. Wschr., 1892, 18: 443.
7. SCHILLING, J. A., and MCKEE, F. W. Experimental hepatic-portal arteriovenous fistulae. Surgical Forum 1953. American College of Surgeons. Vol. IV, p. 392, Philadelphia and London: W. B. Saunders Co., 1954.
8. SCHILLING, J. A., MCKEE, F. W., and WILT, W. Experimental hepatic-portal arteriovenous anastomoses. Surg. Gyn. Obst., 1950, 90: 473.
9. SELDINGER, S. I. Catheter replacement of the needle in percutaneous arteriography. Acta radiol., Stockh., 1953, 39: 368.
10. STRICKLER, J. H., LUFKIN, N., and RICE, C. O. Hepatic portal arteriovenous fistula. Surgery, 1952, 31: 583.
11. WHEELER, H. B., and WARREN, R. Duodenal varices due to portal hypertension from arteriovenous aneurysm. Ann. Surg., 1957, 146: 229.

THE MANAGEMENT OF MASSIVE RECTAL PROLAPSE

JOHN A. PALMER, M.D., F.R.C.S.(C), Toronto, Canada

In 1912 Moschcowitz wrote a classical article on massive prolapse of the rectum in which attention was drawn to the abnormally deep rectovaginal or rectovesical pouch which invariably is present in this condition. He considered this pouch to be the sac of a sliding hernia and the prolapse to be due to a progressive weakening and stretching of the pelvic fascia and levator ani muscles which allowed eventual protrusion of the hernia through the anal sphincter. He demonstrated at operation that pressure on the anterior rectal wall in the depths of the pouch of Douglas would cause the rectum to separate the puborectalis, dilate the anal sphincter, and then prolapse through the anus (Fig. 1).

The Moschcowitz operation was based upon this concept, and in its description he stated: "Silk sutures are passed circularly around the cul de sac of Douglas, and tied . . . until practically the entire pouch of Douglas is obliterated. It is advisable, and I always try to include in my suture the pelvic fascia, particularly that part which covers the levator ani; how often I really succeed in doing this I am not in a position to state. (Theoretically, it would be better to split the peritoneum in the depth of the cul de sac, and to suture the fascia first . . .)."

Graham accepted Moschcowitz' concept and extended the procedure which he suggested as being ideal. He opened the peritoneal sac, identified the ureters, and approximated the medial borders of the levator ani and its fascia in front of the rectum. The redundant peritoneum in the cul-de-sac was excised and closed at a higher and normal level. Thus, the principles of hernial repair were followed. The sac was excised and the musculofascial defect was repaired.

The Moschcowitz-Graham operation has been the procedure used most commonly at the Toronto General Hospital since 1939. It is of interest that the 3 patients treated by this method and reported by Graham in 1942 had no recurrence.

From the Department of Surgery, University of Toronto and the Toronto General Hospital, Toronto.

RECTOSIGMOIDECTOMY

Elsewhere, however, particularly in Britain, the influence of Miles and Gabriel has made rectosigmoidectomy, a perineal pull-through procedure, the popular method of treatment. Hughes, in 1949, reviewed the results in 150 patients with prolapse treated by rectosigmoidectomy and found that in 60 per cent prolapse had recurred, that in 46 per cent there was incontinence, and that in only 14 per cent was the result considered good.

The defects in the operation are failure to repair the musculofascial defect, the impossibility of adequately excising the peritoneal sac from below, and the danger of incontinence due to the low resection and anastomosis.

Gabriel is now attempting to approximate the levator ani from below as part of the procedure. However, even in his hands this appears unsatisfactory, and dissections in the autopsy room further prove that it is difficult and uncertain.

OTHER PERINEAL OPERATIONS

Other operations by the perineal route have an even worse record. After the Lockhart-Mummery operation of posterior rectal fixation by packing the presacral space almost all prolapses recur. In one series of 30 cases, 1 patient died and 29 had a recurrence. The Delorme procedure (Fig. 2), in which the mucosa of the prolapsed bowel is excised and the muscular layer "accordion pleated" by numerous sutures, has a high recurrence rate. Eight patients were treated by this procedure at the Toronto General Hospital. Four patients had recurrence, 1 died, and in 3 the procedure was successful until death, 1 to 3½ years later. The sphincter tone was made worse in 3 cases.

PATIENTS TREATED AT THE TORONTO GENERAL HOSPITAL

Fifty-three patients with rectal prolapse have been treated during the past 20 years, from 1939 to 1958. Of these, 37 were women and 16 were men—a larger number of men than the 6 to 1 ratio usually quoted. As in other reports, the

average age of the men was lower than that of the women, averaging 44 years in men and 60 years in women. Childbirth did not appear to be a predisposing factor. An interesting feature not previously noted was a distribution of the cases into two main age groups (Fig. 3).

The first group consisted of young people between the ages of 15 and 30, averaging 23 years of age, with an equal sex distribution. Members of the second group were aged 45 to 75 years, with an average age of 64 and a preponderance of women. It is possible that prolapse developed in the younger age group because of a congenital defect in the pelvic diaphragm or the peritoneal reflection. Three of these patients had gross defects in this area, including vaginal atresia and absent or grossly deficient levator ani muscles. The older patients would fit into the hernia-prone group in advancing years with its associated musculofascial weakening.

It has been noted that patients with rectal prolapse may have psychopathic personalities. Except for 2 rather odd individuals, the remainder did not exhibit gross psychologic upsets discernible to a surgeon.

PERINEAL OPERATIONS

In general, the results of the various perineal operations have been discouraging. Of the 17 patients so treated, only 6 are known to have had a satisfactory result, and the longest follow-up in these patients was 5 years. The Delorme procedure was reserved mainly for the old and infirm. It is questionable whether this procedure is indicated even in this group, in that recurrence is frequent and incontinence a problem.

It is our opinion that the simple Thiersch operation offers excellent palliation in these elderly people whose declining years are made miserable by repeated or persistent prolapse, leak of mucus, bleeding, and incontinence. In this series, 7 such patients were considered too old or frail for operation. However, during the past 2 years, the value of the Thiersch operation has been appreciated and 3 such patients were treated by this method. In these cases, prolapse has been controlled and incontinence greatly improved (Fig. 4).

THE MOSCHCOWITZ-GRAHAM OPERATION

In contrast to the various perineal procedures, the results in the patients treated by the Moschcowitz-Graham operation have been very good. Twenty-three patients have been operated upon during the past 20 years and none of these has suffered recurrence. There have been no significant morbidity and no deaths.

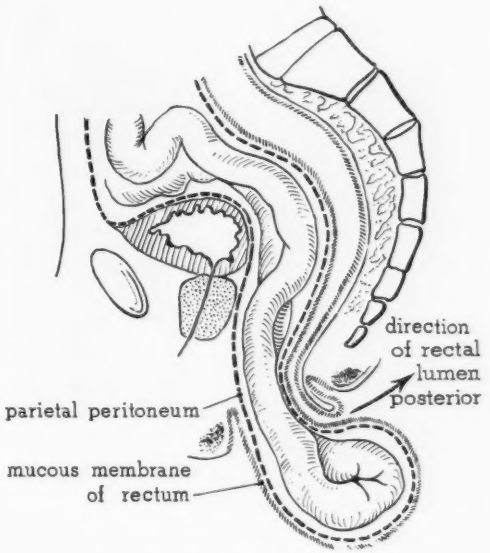


FIG. 1. Diagram of peritoneal pouch.

Although the operation has been well known since it was described by Graham in 1942, it has not become popular. Recently, however, Goligher reported on 23 patients treated by this method during the past 7 years in whom there were no recurrences.

The objection to the operation has been the difficulty of repair in the bottom of the pelvis and actual doubt as to the feasibility of suturing the puborectalis muscle in front of the rectum. Dunphy stated, "The frayed out levator cannot be sutured." Ripstein wrote, "The levator muscles are so thin and friable that they do not form an adequate pelvic support."

However, it has been my experience, with few exceptions, that, provided adequate mobilization of the rectum is carried out, the puborectalis muscle may be visualized without difficulty and sutured with confidence. In 3 patients a rather thin and atrophic levator muscle was reinforced by fascial sutures and in 3 instances the levator ani was sutured behind rather than in front of the rectum.

Despite the feasibility of suturing the levators,

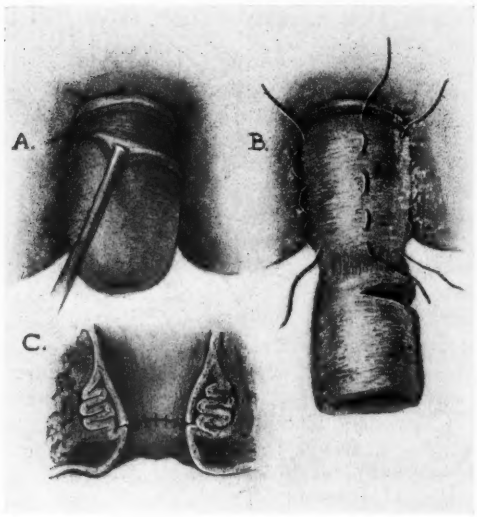


FIG. 2. Details of the Delorme operation.

it must be admitted that such a repair would not be looked upon with much confidence at other hernial sites. It has been suggested that prolapse is cured by fibrous fixation of the rectum to the sacrum and pelvic structures occasioned by the extensive mobilization required for visualization and suture of the levators. Indeed, it has been noted by many surgeons that the rectosigmoid, which remains after anterior resection, becomes very firmly attached to the neighboring structures. This observation led

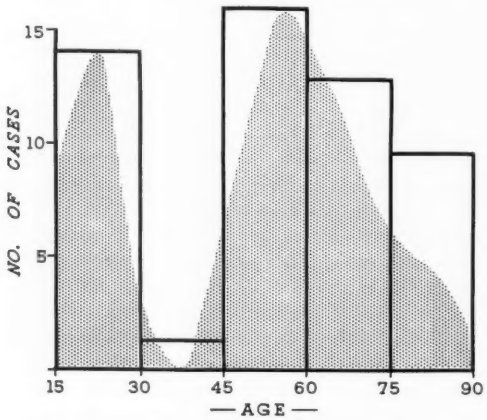


FIG. 3. Age distribution of patients with rectal prolapse.

Mills, in 1947, to advocate for prolapse the mobilization of the rectum as for abdominoperineal resection, the excision of the redundant peritoneum, and a temporary colostomy. Similarly, Muir has practiced anterior resection for prolapse during the past 9 years with no reported recurrences. Anterior resections have been performed in 3 patients during the past 4 years at the Toronto General Hospital with no recurrences to date. However, it would seem that the inconvenience of a colostomy requiring a two stage procedure and the increased risk of anterior resection would make the Moschcowitz-Graham operation the procedure of choice at the present time.

It must be admitted, however, that the extensive freeing of the rectum may be all that is necessary for the cure of prolapse and that the most difficult step in the operation—the suture of the puborectalis muscle—may be unnecessary. The danger of omitting this step would be the failure to control the prolapse during the early postoperative period and the risk of less satisfactory long term results.

The technique of the Moschcowitz-Graham operation practiced at present is essentially the same as that described by Graham in 1942. The abdomen is opened, as for an abdominoperineal resection, through a left paramedian incision extending to the pubis. As Moschcowitz clearly described, the most remarkable finding is the narrow, deep rectovaginal or rectovesical pouch. This pouch with its redundant peritoneum has opened up the rectovaginal septum and extends to the levator ani muscles. It is obvious that to divide the peritoneum in the depths of the pouch at this stage in order to repair the levators would be extremely difficult if not hazardous.

The peritoneum is incised laterally along the margin of the pouch. Both ureters are identified and followed distally. The peritoneal incision is then extended anteriorly along the midposterior surface of the uterus or the base of the bladder in the male. It is easier to see and work in the pelvis if at this stage the peritoneum overlying the posterior border of the bladder or uterus is tacked to the lower limit of the incision.

The rectum is now mobilized as for an abdominoperineal resection. It is of interest to note that in most cases the peritoneal reflection from the sacrum and the rectum is lower than usually seen and the mesorectum may have a peritoneal investment similar to that of the

sigmoid to the level of the sacrococcygeal junction. In freeing the rectum posteriorly to the level of the levator ani muscles, care should be taken to avoid injury to the presacral nerves.

The peritoneal pouch is then freed anteriorly to the level of the anorectal ring, mainly by blunt dissection. Visualization is improved if the redundant peritoneum of the pouch is excised to its margin of attachment to the rectum.

Remaining to be divided to insure adequate exposure are the lateral ligaments. In patients with long-standing massive prolapse, particularly of the intussuscepting type with a low posterior reflection as well as a deep anterior pouch, the lateral ligaments may be almost absent.

After division of the lateral ligaments, the puborectalis sling should be defined and a decision made as to the placing of sutures (Fig. 5). The medial borders of the puborectalis muscle are then approximated by interrupted No. 00 black silk sutures. Usually, the repair is made anterior to the rectum, but since 1947 occasional repair has been made by placing the sutures posterior to the rectum. The posterior repair replaces the anorectal area to a more normal position. This variation in the operation was first performed by Wookey. Probably the most precise repair is the placing of a single figure-of-eight suture anterior to the rectum and then approximating the muscle posteriorly. By placing sutures anteriorly and posteriorly, an opening just adequate for the rectum may be more easily gauged.

The rectum is then tacked by 3 or 4 sutures to the puborectalis and, also, to the fascia overlying the sacrum with the expectation that postoperative fibrosis will maintain this position.

The peritoneum anteriorly and laterally is then approximated and a new peritoneal floor is made at a normal level. A portion of the original peritoneal floor remains attached firmly to the anterior surface of the rectum below the reconstituted peritoneal floor. A Penrose drain is usually placed extraperitoneally to the area of repair.

THE PROBLEM OF INCONTINENCE

Twenty of the 23 patients treated by the Moschcowitz-Graham operation have been reexamined and the remainder contacted by letter. The lack of recurrence has been pleasing. However, one of the perplexing problems frequently

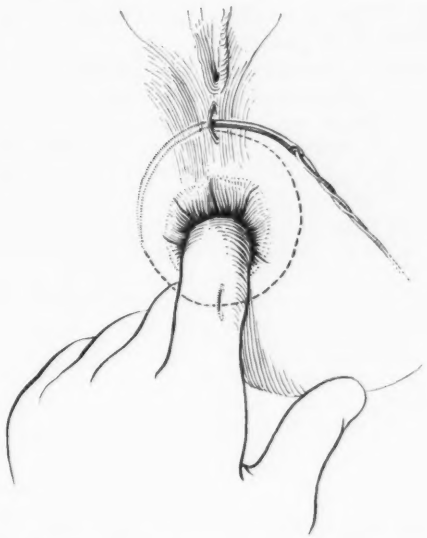


FIG. 4. The Thiersch operation. A No. 24 steel wire is passed circularly around the anus and tied loosely over the index finger.

associated with prolapse is rectal incontinence. Re-examination revealed little justification for the optimism with which Graham expected the eventual return of normal control.

Rectal incontinence was present pre-operatively in 7 of the patients treated by perineal procedures and in 8 of those treated by the Moschcowitz-Graham operation. Incontinence

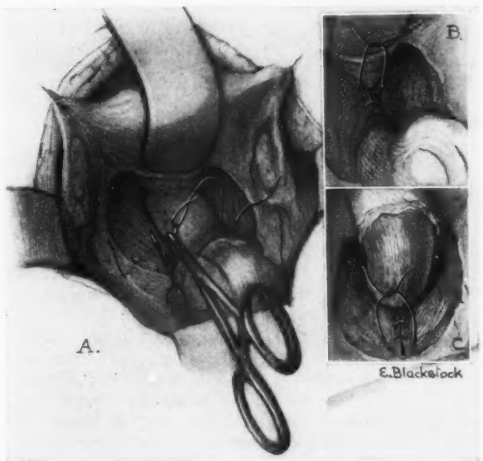


FIG. 5. The Moschcowitz-Graham operation.

occurred in two main groups of patients: those who had had prolapse for a year or more with frequent or almost continual prolapse, occurring in the young as well as in the older age group, and a group made up mainly of the old and infirm. In the latter group, there is good reason to believe that a lax sphincter was present prior to prolapse and probably contributed to eventual prolapse. If rectal control was normal prior to operation, there was no incontinence postoperatively whether treatment was by an abdominal or perineal operation. However, in those who had poor control and were treated by perineal procedures, incontinence was made worse in 5 of the 7 patients.

Of the 8 patients with incontinence treated by the Moschcowitz-Graham operation, 3 regained normal control; the others remained much the same or had slight improvement with loss of control of flatus or liquid feces only. The 3 who returned to normal were all from the younger age group. Although more cases are required for follow-up study; it would appear that sphincter control in the younger patient has a better chance of returning to normal or near normal than in the older patient.

Of interest is the possibility of improving sphincter control by suturing the puborectalis muscle posterior, rather than anterior, to the rectum. Unfortunately, this variation of the operation has not been used as yet in a case associated with incontinence. The puborectalis sling is recognized as an integral and important part of the sphincter mechanism and its suture posterior to the rectum would tend to produce a better sling effect at the anorectal ring and perhaps enhance anal control.

SUMMARY

Fifty-three patients with massive prolapse of the rectum treated during the past 20 years have been reviewed in the present communication.

Prolapse occurred in two main age groups: a younger group, the prolapse probably caused by congenital defects in the peritoneal attachments and the pelvic diaphragm, and a group of older patients at the age of musculofascial weakening. The results of the various perineal procedures were unsatisfactory, in that recurrence was frequent.

Twenty-three patients were treated by the Moschcowitz-Graham operation during this 20 year period without recurrence. Since no reported method has given such satisfactory results over as long a period, the technique of the operation as originally described by Graham was reviewed.

The problem of associated incontinence was discussed and a variation of the operation was suggested as a possible means of improvement in its treatment. It is suggested that the Moschcowitz-Graham operation is the procedure of choice for patients of acceptable operative risk. If the patient is old or feeble and judged unable to withstand an abdominal operation, the simpler Thiersch procedure is advised.

REFERENCES

1. Gabriel, W. B. Principles and Practice of Rectal Surgery. 4th ed. Springfield, Ill.: Charles C Thomas, 1948.
2. Goligher, J. C. The treatment of complete prolapse of the rectum by the Roscoe Graham operation. Brit. J. Surg., 1958, 45: 323.
3. Graham, Roscoe R. Operative repair of massive rectal prolapse. Ann. Surg., 1942, 115: 1007.
4. Hughes, E. S. R. Discussion on prolapse of the rectum. Proc. R. Soc. M., Lond., 1949, 42: 1007.
5. Mills, J. D., and Lawler, W. R. Prolapse of rectum. Canad. M. Ass. J., 1956, 75: 5.
6. Moschcowitz, A. V. The pathogenesis, anatomy, and cure of prolapse of the rectum. Surg. Gyn. Obst., 1912, 15: 7.
7. Muir, E. G. Rectal prolapse. Proc. R. Soc. M., Lond., 1955, 48: 33.
8. Ripstein, C. B. Treatment of massive rectal prolapse. Am. J. Surg., 1952, 83: 68.

REPAIR OF THE INJURED LARYNX FOLLOWING DESTRUCTION OF THE CRICOID CARTILAGE

BENJAMIN F. RUSH, JR., M.D., F.A.C.S., Baltimore, Maryland

IT IS GENERALLY AGREED that the crushed larynx should be repaired as soon as possible after the injury. At that time the soft fragments of the cartilages can be molded over an internal splint of plastic or rubber, mucosal tears can be repaired, and the organ will heal something in the fashion of internally splinted fractures of the nasal bones. Should repair of the crushed larynx be long delayed, granulation tissue, scarring, and laryngeal stenosis may make repair a difficult, tedious, and many staged task. If a patient has had a neglected crushing injury of the larynx and is found, in addition, to have lost the majority of the ring of the cricoid cartilage, many investigators have noted that repair is impossible and that the patient will be condemned to live with a permanent tracheostomy. Jackson and Jackson have stated "... loss of cartilage is the most serious complication as regards cure. If the stiffening that holds the larynx open is gone, the larynx is practically obliterated and restoration of a permanent lumen is extremely difficult."

Three years ago, a patient was admitted to the Baltimore City Hospitals with a crushing injury of the larynx and loss of the majority of the cricoid cartilage, repair of which was long delayed. It was possible to devise an operation for this patient which restored his voice and laryngeal continuity in a one stage procedure.

CASE REPORT

A 26 year old steel worker was admitted to the accident room on 8 June 1957. He had been in an automobile accident 1 hour prior to admission. A reconstruction of the circumstances indicates that he was sitting next to the driver when the car hit a pole. The patient made a violent exit through the windshield, face foremost. On admission he was found to have a small but very deep laceration in the lower midline of the neck. Frothy blood and air were coming through the laceration. It was evident that he had sustained an open injury of the larynx or trachea, and a tracheostomy tube was immediately placed through the traumatic wound and into the trachea, relieving his difficult respirations. His pulse was 120 beats per minute and blood pressure 80/40 millimeters of mercury. A transfusion was given, and the patient was examined further. He had sustained a fracture of the nose and a long laceration over the left knee. He was dazed and had a slight retrograde amnesia but neurologic findings were otherwise unremarkable. The patient was admitted to the hospital, and on the following morning it became apparent that, in addition to the laryngeal injuries, the patient also had a fairly large esophageal fistula which drained not only through the external wound in the neck but into the trachea as well. By the time this complication was discovered, it was considered to be too late to permit primary repair of the esophageal defect or to reconstruct the larynx. Mirror examination of the larynx, both from above and through the tracheostomy site, showed fractures of the thyroid and cricoid cartilages. A large piece of cartilage was noted wedged in the larynx in the area of the cricoid, and both vocal cords were paralyzed. A drain was placed into the neck laceration down to the site of the tear in the esophagus. The esophagocutaneous portion of the fistula continued to drain copiously.

Six days after admission a gastrostomy was performed and the patient was started on feedings by stomach tube. Lipiodol studies at 2 weeks and at 1 month after admission showed that the tracheoesophageal fistula still persisted. The patient's lungs were kept clear by repeated tracheal toilets through the tracheostomy tube.

By the fifth week after admission, both the esophagolaryngeal and the esophagocutaneous fistulas seemed to have closed. The patient was able to take fluid and water by mouth without difficulty.

During the first few weeks in the hospital the patient could talk in a whisper when the tracheostomy tube was closed with a finger, but approximately 6 weeks after injury he lost this ability completely. On 19 August 1957, direct laryngoscopy revealed that the arytenoid cartilages were in normal position and the vocal cords were fixed and appeared scarred in semi-abduction. Immediately beneath the cords a severe stenosis was noted. It was impossible to pass a No. 9 wax tipped bougie through the larynx. The pyriform areas and the esophageal entrance were entirely normal. Lipiodol was inserted into the larynx 2 months after the injury, and roentgenograms showed complete obstruction of the larynx (Fig. 1). The laryngeal lumen, just beneath the cords, had collapsed, and the major portion of the cricoid appeared to be severed from the larynx and retracted down into the neck. It was obvious that if the patient was to re-

From the Departments of Surgery of The Johns Hopkins Hospital, the Baltimore City Hospitals, and The Johns Hopkins University School of Medicine, Baltimore.

FIG. 1. The lipiodol study shown here was made 8 weeks after the injury and demonstrates the complete laryngeal stenosis that has supervened. The larynx tapers from just beneath the cords to a point of complete obstruction. The major portion of the cricoid cartilage lies well below the larynx from which it was severed. The metal tag on the skin is at the normal level of the cricoid anteriorly. The tracheostomy tube was removed to facilitate the roentgenographic study.

gain his voice and airway, reconstruction of the larynx was required.

Exploration of the larynx and trachea was carried out on 24 September 1957, 3½ months after injury. A transverse incision was made across the neck at about the level of the cricoid cartilage. On dissecting down to the site of the injury it was discovered that the entire ring of the cricoid cartilage had been severed from the larynx just below the level of the arytenoid cartilages and that the lower portion of the thyroid cartilages was badly damaged and crushed toward the midline (Fig. 2a). The collapsed segment composed of cricoid cartilage and upper trachea measured approximately 3 to 4 centimeters in length. An attempt was made to open this segment, but no lumen could be found in the scarred mass. The right recurrent laryngeal nerve was picked up and traced into the scar where it was found to be divided. No portion of the proximal part of the nerve could be found. The left recurrent laryngeal nerve was not located but, in view of the knowledge that both cords were paralyzed prior to the procedure, it was presumed that it also had been transected by the original injury.

The entire block of scarred and crushed tissue which included the remnants of the ring of the cricoid cartilage was resected. The small segment of the posterior cricoid to which the arytenoid cartilages were still attached was left in place. The lower portions of both thyroid cartilages likewise had to be resected, since they had been crushed in such a way that they obstructed the lower larynx. Thus, the entire larynx from a point approximately 5 millimeters below the true cords was resected. The trachea was dissected away from the underlying esophagus and mobilized down into the mediastinum, the scarred upper end was resected, and the first and second tracheal rings were removed. The trachea was then quite easily brought up and apposed to the remaining larynx (Fig. 2b). The posterolateral portion of the uppermost tracheal cartilage and the tracheal membrane were sutured to the remaining posterosuperior fragment of the cricoid cartilage with interrupted sutures of No. 32 stainless steel wire. The mucosa was not included in this first layer closure. A small bite of prevertebral fascia was included in each suture. Next, the mucosa was closed with closely placed interrupted No. 4-0 chromic catgut sutures. After completion of the two posterior layers, a thin-walled segment of large polyethylene tubing was inserted as a stent. This tubing was approximately 4 centimeters in length and was placed to lie just beneath the vocal cords and through the line of anastomosis. One of the chief problems was that the trachea below, a round structure, was being anastomosed to the larynx above, an essentially triangular structure made up of the two plates of thyroid cartilage, and the small remaining posterior strut of cricoid cartilage. The thin-walled polyethylene tube tended to assume a triangular conformation in the larynx and resume its normal round shape in the trachea. The mucosal closure was completed laterally and anteriorly. At the most anterior point a laryngofissure had been necessary through the thyroid cartilage and there was no mucosa in this area for a distance of about 4 millimeters. The closure was continued, and the trachea was anastomosed to the thyroid cartilage laterally and anteriorly with stainless steel sutures. The stent was held in place in the trachea with stainless steel wires which passed through the trachea and the stent and back again on either side to the skin where they were tied over sterile buttons. The strap muscles were then reapproximated over the larynx, and the skin of the neck was closed. A small drain was placed down to the site of anastomosis to avoid the dangers of emphysema from air leakage at this site. The patient withstood the procedure well and was returned to the ward in good condition.

The postoperative course was smooth and uncomplicated. The drain was removed from the neck wound 24 hours postoperatively and the patient was discharged from the hospital on the twenty-first postoperative day with the neck wound well healed and the stent still present in the larynx. Two and a half months after operation, the patient was readmitted, and the stent was removed from the larynx. Direct laryngoscopy at this time revealed the area of anastomosis just beneath the cord to be smooth and well healed and a minimal formation of granulation tissue just beneath the anterior commissure where the mucosal closure was incomplete. After removal of the stent the tracheostomy was corked and the patient was followed up in the Outpatient Department. Approximately 4 months after operation he was read-

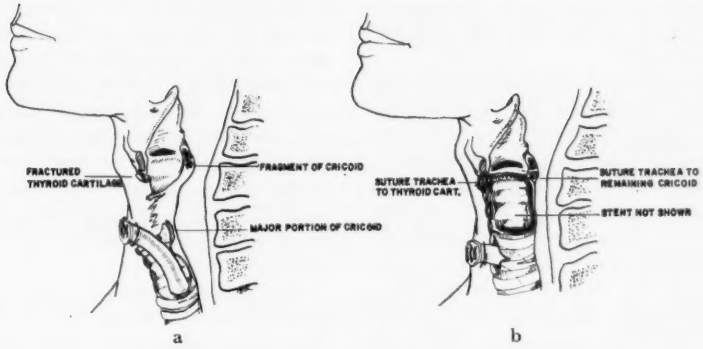


FIG. 2. a, Stenosis of injured larynx. The major portion of the cricoid cartilage has been severed from the larynx and has retracted down the neck. A small fragment of the posterior portion of the cricoid remains with the main body of the larynx. The intervening space is filled with scar, and there is obliteration of the lumen. The lower portion of the thyroid cartilage is fractured. b, Repair of larynx. Cut-away drawing of the completed repair. The block of scar tissue and obliterated lumen separating the upper and lower portions of the larynx have been excised. The trachea has been drawn up and anastomosed to the remaining larynx. The anastomosis consists of an inner interrupted mucosal layer and an outer layer of interrupted sutures which pass through the annular ligaments and around the tracheal cartilages. The patient is now well with a husky but useful voice and a patent airway 3 years postoperatively.

mitted for the third and last time. The tracheostomy was removed and observations were made for a period of 24 hours after which he was discharged.

This patient has been followed up for the last 3 years in the Outpatient Department of the Baltimore City Hospitals. Indirect laryngoscopy shows that the vocal cords remain scarred and fixed. The patient's voice is hoarse and low but clearly understandable and useful. If the patient finds it necessary to increase the pitch or loudness of his voice he has learned to squeeze the residual larynx with his fingers, forcing the cords somewhat closer together by external pressure. This pressure tends to increase the volume of the sound produced. The patient has had no difficulty in breathing and has been fully employed in his occupation as a steelworker for the last 2½ years.

DISCUSSION

Despite the facts that the portion of the cricoid cartilage which forms the complete ring was lost and that both recurrent nerves had been divided, it was possible to reconstruct the larynx in such a way as to produce a usable voice and to avoid the complications of formation of granulation tissue and further stenosis. It is believed that the following circumstances in this particular patient contributed to the success of the operative procedure: (1) Despite the loss of the complete cricoid ring, a small portion of the posterior "shield" of the cricoid cartilage was left, which, lying between the two plates of the thyroid cartilage, prevented them from collapsing. (2) Although the patient had complete vocal cord paralysis which under normal circumstances might have led to the ultimate approximation of the cords in the midline and obstruction, in this instance the fact that the cords had become involved in the scarring of the larynx itself and had become totally fixed and immovable prevented the development of this complication.

Two details of the operation seem, on reflection, to be of importance: (1) The round shape of the stent prevented complete closure of the laryngofissure in the midline. The anterior commissure of the cords was thus spread several millimeters apart. At the time, this spread was somewhat distressing but, in retrospect, it is believed that it contributed to the widening of the glottic chink and insured a more adequate airway. (2) It is thought that the mucosa-to-mucosa approximation contributed to the prevention of formation of granulation tissue and stenosis at the suture line. This same principle has proved of considerable value in preventing stenosis of the suture line in ileocutaneous, esophagogastric, and ureteroileal anastomoses.

It may not have been necessary to include the tracheal rings in the outer layer of the anastomosis. Cantrell has demonstrated that the chief strength of the trachea in holding sutures lies in

the tough intercartilaginous fascia. Suture material usually cuts through the soft tracheal cartilage rather readily.

The success of this procedure suggests several other possibilities in injuries of the larynx in which this technique might be applicable. Should the cords be paralyzed but not fixed, an adequate airway may be obtained by lateral transplantation of the arytenoid by modifications of the method of King. This procedure may be supplemented by anterior laryngofissure and spreading the anterior commissure over a stent. This maneuver seemed helpful to this patient and had previously been suggested by Bryce. If all parts of the cricoid including the posterior superior portion are lost, it might be possible to replace the posterior portion, holding the thyroid cartilages apart with a bone graft as Herzog and Nissen have done so successfully in the repair of other tracheal defects.

SUMMARY

A 26 year old male patient suffered complete destruction of the portion of the cricoid forming the ring, as the result of an automobile accident. A simultaneous esophageal laceration was not recognized until the development of a laryngoesophageal and laryngocutaneous fistula. The resulting infection prevented early reconstruction. Stenosis of the larynx resulted, and obstruction of the airway became complete by 4 weeks after the injury. In addition to the tracheal injury, there was bilateral cord paralysis. It was possible to treat this combination of injuries and complications by a block excision of the cricoid cartilage—with the exception of a small sliver of its posterior superior portion—the scar tissue closing the larynx and the upper two rings of the trachea, and with reanastomosis of the trachea to the remaining larynx over a stent. Two years after operation, the patient has no dyspnea or respiratory obstruction, and he has a usable voice.

The important points in the repair were the anterior laryngofissure, the spreading of the anterior commissure to ensure an adequate airway, and the mucosa-to-mucosa anastomosis carried out during the two layer closure, ensuring the avoidance of formation of granulation tissue.

REFERENCES

1. Bryce, D. P. Traumatic laryngotracheal injury. Canad. M. Ass. J., 1956, 75: 400.
2. Cantrell, J. Personal communication.
3. Herzog, H., and Nissen, R. Erschlaffung und exspiratorische Invagination des membranoesen Teils der intrathorakalen Luftroehe und der Hauptbronchien als Ursache der asphyktischen Anfaelle beim Asthma bronchiale und bei der chronischen asthmoiden Bronchitis des Lungen-emphysems. Schweiz. med. Wschr., 1954, 84: 217.
4. Jackson, C., and Jackson, C. L. Lewis' Practice of Surgery. Vol. IV, chap. 7. Hagerstown, Md.: W. F. Prior Co., Inc., 1945.
5. King, B. T. New and function restoring operation for bilateral abduction cord paralysis; preliminary report. J. Am. M. Ass., 1939, 112: 814.

THE SURGEON'S LIBRARY

The Book Shelf

JOSEPH LISTER AND THE OLD EDINBURGH INFIRMARY AS DESCRIBED BY THE POET WILLIAM ERNEST HENLEY

PETER D. OLCH, M.D., Bethesda, Maryland, and

LLOYD M. NYHUS, M.D., F.A.C.S., Seattle, Washington

ALWAYS OF INTEREST to physicians is the occasional expression in the lay literature of the patient's views and interpretations of his encounter with the medical profession. A rare opportunity arises when such views and interpretations are made by a literary figure and involve a prominent individual or institution within the field of medicine. Such an opportunity occurred when the poet, William Ernest Henley was a patient of Joseph Lister in the latter's surgical ward of the Old Edinburgh Infirmary for 20 months (1873–1875). Henley's reactions to the hospital, his fellow patients, physicians, nurses, and surgery are beautifully preserved in his combined group of verses entitled "In Hospital" (7). These 28 collected verses were written during the latter part of his hospital stay and were published initially in the magazine *Cornhill* by Leslie Stephen (1).

William Ernest Henley (Fig. 1) is perhaps most familiar as the author of the poem "Invictus" which begins with the lines, "Out of the night that covers me, black as the Pit from pole to pole," and ends, "I am the master of my fate; I am the captain of my soul."

Briefly, Henley was born in 1849 in Gloucester, the son of a bookdealer. As a youth, he read continually and spent little time in the usual boyhood physical activities. At the age of 12 years he was found to have tuberculous arthritis. He was an excellent student and, in 1867, at the age of 18 years he passed the entrance examinations for Oxford. However, his poverty and ill health prevented his entering the college. In 1868 he "accepted the verdict of incompetent surgeons" (2) and his left foot was amputated. After the amputation he returned to Gloucester disillusioned, and in the course of the next 5 years his right foot became progressively involved by the disease. When he was again advised to have an amputation in 1873, he "scorned the harsh decree" (3) and set out for Edinburgh and the service of Joseph Lister.

Lister, at this time, was well into his clinical studies with antiseptic agents which he had started in 1865 while occupying the Chair of Surgery at the University of Glasgow. He had returned to the University of Edinburgh in 1869 to take over the Chair of Surgery vacated by his father-in-law, James Syme. Here, his antiseptic principles were somewhat more warmly received though many of his colleagues scoffed at his reasoning and methods. At Edinburgh he had his own 50 bed ward on which his methods and policies were carefully followed. His enthusiastic following was at this time limited to his students and house staff at Glasgow and Edinburgh and isolated centers in Germany. Among the violent antagonists were such eminent figures as James Paget, Sir James Simpson, and Hughes-Bennett, the Professor of Medicine at Edinburgh who

From the Department of Surgery, University of Washington School of Medicine, Seattle.

persistently ridiculed the new doctrine with the cry, "Where are the germs? Show them to us and we will believe . . ." (5). However, through one channel or another, William Ernest Henley heard of the surgeon in Edinburgh who was saving many limbs from amputation and proceeded to the Edinburgh Infirmary and Dr. Lister for treatment of his tuberculous arthritis.

The old Edinburgh Infirmary in which Lister's 50 bed surgical ward for chronic patients was located was opened in 1742 as a high school. In 1832, it was transformed from an educational to a surgical institution with 72 beds, as well as 12 cells for insane persons. There was no running water or plumbing. The heating was by fires and the lighting by gas lamps and candles. The present Royal Infirmary was opened in 1879, and the Surgical Hospital became first the Fever Hospital and later the Engineering Department of the University. As recently as 1949 the building housed the Department of Geography. The corridors of the Old Infirmary had their own peculiar smell—a mixture of stale tobacco smoke, carbolic acid, and boiled beef (6).

One can readily sense the feeling of uncertainty, almost impending doom expressed by the author as he approaches the hospital for admission in August of 1873.

> The morning mists still haunt the stony street;
> The northern summer air is shrill and cold;
> And lo, the Hospital, grey, quiet, old,
> Where Life and Death like friendly chafferers meet.
> Thro' the loud spaciousness and draughty gloom
> A small, strange child—so aged yet so young!—
> Her little arm besplinted and beslung,
> Precedes me gravely to the waiting-room.
> I limp behind, my confidence all gone.
> The grey-haired soldier-porter waves me on,
> And on I crawl, and still my spirits fail:
> A tragic meanness seems so to environ
> These corridors and stairs of stone and iron,
> Cold, naked, clean—half-workhouse and half-jail.

Henley then describes the waiting room or admissions clinic with its hard benches, gloomy interior, and varied patients.

> A square, squat room (a cellar on promotion),
> Drab to the soul, drab to the very daylight;
> Plasters astray in unnatural-looking tinware;
> Scissors and lint and apothecary's jars.
>
> Here, on a bench a skeleton would writhe from,
> Angry and sore, I wait to be admitted:
> Wait till my heart is lead upon my stomach,
> While at their ease two dressers do their chores.
>
> One has a probe—it feels to me a crowbar.
> A small boy sniffs and shudders after bluestone.
> A poor old tramp explains his poor old ulcers.
> Life is (I think) a blunder and a shame.

Henley's initial revulsion to the ward is very realistically expressed in the verse entitled "Interior."

> The gaunt brown walls
> Look infinite in their decent meanness.
> There is nothing of home in the noisy kettle,
> The fulsome fire.
>
> The atmosphere
> Suggests the trail of a ghostly druggist.
> Dressings and lint on the long, lean table—
> Whom are they for?
>
> The patients yawn,
> Or lie as in training for shroud and coffin.
> A nurse in the corridor scolds and wrangles.
> It's grim and strange.
>
> Far footfalls clank.
> The bad burn waits with his head unbandaged.
> My neighbor chokes in the clutch of chloral . . .
> O, a gruesome world!

Shortly after admission to Lister's surgical ward, Henley was taken to surgery where a tuberculous abscess cavity of his remaining foot was drained and curetted. Immediately prior to operation, the author expressed, "Behold me waiting—waiting for the knife. A little while, and at a leap I storm the thick, sweet mystery of chloroform, the drunken dark, the little death-in-life." He continues, "Yet I am tremulous and a trifle sick, and face to face with chance, I shrink a little; my hopes are strong, my will is something weak."

The operating amphitheater seated 400 or 500 people. There was a large ground area surrounded by chairs for a dozen or more distinguished visitors and these were often filled. Four dressers in blue checked aprons would bring in the patient on a long wicker basket and place him on the table. Henley describes his operation as follows:

> You are carried in a basket,
> Like a carcase from the shambles,
> To the theatre, a cockpit
> Where they stretch you on a table.
>
> Then they bid you close your eyelids,
> And they mask you with a napkin,
> And the anaesthetic reaches
> Hot and subtle through your being.
>
> And you gasp and reel and shudder
> In a rushing, swaying rapture,
> While the voices at your elbow
> Fade—receding—fainter—farther.

The recovery from the chloroform anesthesia is described in the verse, "After."

Like as a flamelet blanketed in smoke,
So through the anaesthetic shows my life;
So flashes and so fades my thought, at strife
With the strong stupor that I heave and choke
And sicken at, it is so foully sweet.
Faces look strange from space—and disappear
Far voices, sudden loud, offend my ear—
And hush as sudden. Then my senses fleet
All were a blank, save for this dull, new pain
That grinds my leg and foot; and brokenly
Time and the place glimpse on to me again;
And, unsurprised, out of uncertainty,
I wake—relapsing—somewhat faint and fain,
To an immense, complacent dreamery.

After operation Henley spent many months convalescing on the surgical ward. Initially, these were dark weeks of uncertainty, expressed so vividly in the poem entitled, "Vigil."

Lived on one's back,
In the long hours of repose,
Life is a practical nightmare—
Hideous asleep or awake.

Shoulders and loins
Ache— — —!
Ache, and the mattress,
Run into boulders and hummocks,
Glows like a kiln, while the bedclothes—
Tumbling, importunate, daft—
Ramble and roll, and the gas,
Screwed to its lowermost,
An inevitable atom of light,
Haunts, and a stertorous sleeper
Snores me to hate and despair.

All the old time
Surges malignant before me;
Old voices, old kisses, old songs
Blossom derisive about me;
While the new days
Pass me in endless procession:
A pageant of shadows
Silently, leeringly wending
On . . . and still on . . . still on!

. . . The next man to me
Turns with a moan; and the snorer,
The drug like a rope at his throat,
Gasps, gurgles, snorts himself free, as the nightnurse,
Noiseless and strange,
Her bull's eye half-lanterned in apron
(Whispering me, "Are ye no sleepin' yet?"),
Passes, list-slippered and peering,
Round . . . and is gone.

Sleep comes at last—
Sleep full of dreams and misgivings—
Broken with brutal and sordid
Voices and sounds that impose on me,
Ere I can wake to it,
The unnatural, intolerable day.

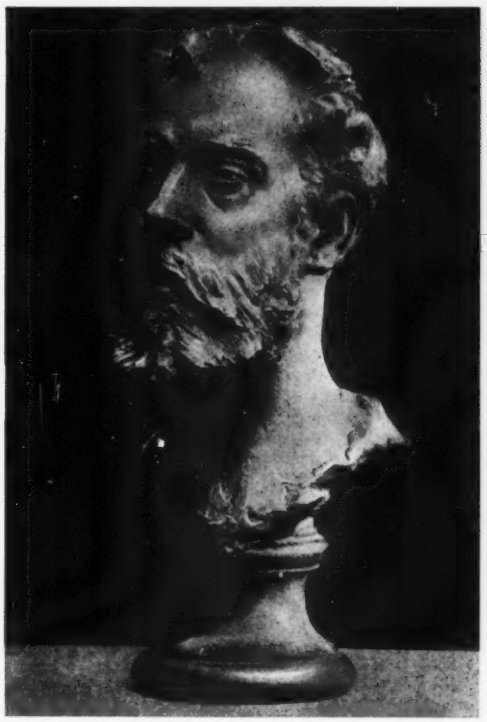


FIG. 1. A bronze bust of William Ernest Henley by Auguste Rodin (1886). Courtesy of Charles Scribner's Sons.

As the months rolled by and Henley's condition slowly but surely improved, his ability to transcend his suffering and to gain mental release in an interest in those about him was manifest in the numerous verses that comprise verbal portraits of his fellow patients, the scrubwoman, the nurses, physicians, and Lister himself. A sailor tells of blockade-running in the American war, of mud and chains, and Negroes on the wharf at Charleston. The ploughman in his "crackling, hackling" voice sings "of bonnie lasses keeping sheep among the heather." The scrubwoman is described as "tall and gaunt, and in her hard, sad face with flashes of the old fun's animation, there lowers the fixed and peevish resignation bred of a past where troubles came apace . . . you shall find no rougher, quainter speech, nor kinder heart."

Mrs. Janet Porter, the head nurse on Lister's surgical ward, by all reports was master of any and all situations and was quick to give a

Scotch tongue lashing to anyone who crossed her path, including the "chief" himself. She is described by Henley in his verse entitled, "Staff Nurse: Old Style."

> The greater masters of the commonplace,
> Rembrandt and good Sir Walter—only these
> Could paint her all to you: experienced ease
> And antique liveliness and ponderous grace;
> The sweet old roses of her sunken face;
> The depth and malice of her sly, grey eyes;
> The broad Scots tongue that flatters, scolds, defies;
> The thick Scots wit that fells you like a mace.
> These thirty years has she been nursing here,
> Some of them under Syme, her hero still.
> Much is she worth, and even more is made of her.
> Patients and students hold her very dear.
> The doctors love her, tease her, use her skill.
> They say "The Chief" himself is half-afraid of her.

In his description of a young staff nurse, Henley refers to a young lady

> Blue-eyed and bright of face but waning fast
> Into the sere of virginal decay,
> I view her as she enters, day by day,
> As a sweet sunset almost overpast.

The surgical house officer, who was as much a nurse as a surgeon and physician in those days, is described as

> Bland as a Jesuit, sober as a hymn;
> Humerous, and yet without a touch of whim;
> Gentle and amiable, yet full of fight;
> His piety, though fresh and true in strain,
> Has not yet whitewashed up his common mood
> To the dead blank of his particular Schism.

Lister, who was greatly admired and respected by his housestaff, nurses, students, and patients, is paid great tribute by Henley in the poem entitled, "The Chief."

> His brow spreads large and placid, and his eye
> Is deep and bright, with steady looks that still.
> Soft lines of tranquil thought his face fulfil—
> His face at once benign and proud and shy.
> If envy scout, if ignorance deny,
> His faultless patience, his unyielding will,
> Beautiful gentleness and splendid skill,
> Innumerable gratitudes reply.
> His wise, rare smile is sweet with certainties,
> And seems in all his patients to compel
> Such love and faith as failure cannot quell;
> We hold him for another Herakles,
> Battling with custom, prejudice, disease,
> As once the son of Zeus with Death and Hell.

After 20 months of hospitalization, Henley was discharged to a nursing home in April 1875 for several months. However, he was able to take carriage rides through the countryside on weekends with his recently acquired friend, Robert Louis Stevenson, who also had tuberculosis. On recovering completely, Stevenson and Henley began a literary association which lasted some few years. Stevenson modeled his character Long John Silver of *Treasure Island* after Henley; "It was the sight of your maimed strength and masterfulness that begat John Silver" (4). In later years Henley became a renowned literary critic and a recognized poet. His followers in later years were known as "Henley's Regatta" and included such literary figures as W. B. Yeats and Rudyard Kipling.

These collected verses compiled by Henley under the title, "In Hospital" were the author's first poetic effort and were important in the field of literature as one of the first examples of free verse in this particular period.

In closing this commentary on Henley and his encounter with Lister and the Old Edinburgh Infirmary, one can view his most familiar poem, "Invictus" as an epilogue to the hospital drama. Interpreted in this light, it acquires a significance far beyond its value as an isolated unit. It appears to mark the invalid's triumph over physical handicap.

> Out of the night that covers me,
> Black as the Pit from pole to pole,
> I thank whatever gods may be
> For my unconquerable soul.
>
> In the fell clutch of circumstance
> I have not winced nor cried aloud.
> Under the bludgeonings of chance
> My head is bloody, but unbowed.
>
> Beyond this place of wrath and tears
> Looms but the Horror of the shade,
> And yet the menace of the years
> Finds, and shall find, me unafraid.
>
> It matters not how strait the gate,
> How charged with punishments the scroll,
> I am the master of my fate;
> I am the captain of my soul.

REFERENCES

1. Buckley, Jerome H. William Ernest Henley. 1st ed., p. 53. Princeton: Princeton University Press, 1945.
2. Ibid., p. 40.
3. Ibid., p. 41.
4. Ibid., p. 99.
5. Cameron, Hector C. Joseph Lister, Friend of Man. 1st ed., p. 82. London: W. Heinemann Ltd., 1948.
6. Guthrie, Douglas. Lord Lister, His Life and Doctrine. 1st ed., p. 73. Edinburgh: E. and S. Livingstone, Ltd., 1949.
7. Henley, William E. Poems. 19th ed., p. 3. New York: Charles Scribner's Sons, 1919.

Reviews of New Books

THE STORY of the treatment of injury in patients past the age of 60 years is told—in the volume *Trauma in the Aged*.[1] The special circumstances of trauma in our senior citizens are summarized in the excellent opening chapter by Robert H. Kennedy. A distinguished group of authors has contributed to this volume which is edited by Edgar Bick.

The book is divided into five parts. In the first section pathology of trauma in the aged is discussed, and the subjects of shock, preoperative and postoperative care, anesthesia, wound healing, and burns are presented. The second section deals with musculoskeletal injury, including fractures and dislocations. Visceral trauma of the abdomen, thorax, and genitourinary tract is discussed in the third section. The fourth part of the volume covers a variety of subjects related to injuries of the aged. These subjects include craniovertebral injuries, vascular trauma, and injuries of the face and neck. The last part is devoted to the rehabilitation of older people.

This book, in general, is well written and emphasizes the special problems of trauma in the aged. The work should be of value to all physicians who are engaged in the care and treatment of those in the sixth decade of life or beyond.

—*William A. Larmon.*

IT WAS INDEED A PRIVILEGE to review *Selected Papers*,[2] by Sir Geoffrey Jefferson. His classic simplicity of description, literary style, knowledge of history, clinical observation, and ability to report make for delightful and interesting reading. The art of writing is beautifully illustrated in this volume.

A major portion of the book consists of clinical papers. The student of neurosurgical literature is familiar with many, if not most, of these. However, the assembly of 14 in a single volume furnishes a "collector's windfall."

The chapters, which the author classifies under the headings of "Reflections" and "Portraits," constitute an historical survey of neurologic surgery, with development of neurophysiologic thinking and brief bibliographic sketches of the outstanding pioneers in the development of neurology and neurologic surgery. In the section entitled "Neurosurgery," Sir Geoffrey has selected 14 papers on clinical subjects, with particular emphasis on vascular and traumatic lesions, both of which are of special interest to him. Here, his superb literary style enables inspiring and informative reading. The reviewer particularly enjoyed the following: "The Tentorial Pressure Cone," "On the Saccular Aneurysms of the Internal Carotid Artery in the Cavernous Sinus," "The Balance of Life and Death in Cerebral Lesions," and "The Disintegration of Consciousness in Posterior Fossa Lesions." The paper on the "Return to Russia" is of interest, especially because of our present relationship with Russia. The philosophic discussion in "On Being Happy and Liking It," concludes the volume with a delightful flourish.

—*David Cleveland.*

THE ART OF CLINICAL DIAGNOSIS, mastered only by diligence and constant effort, is enhanced greatly by the use of a volume such as *Demonstrations of Physical Signs in Clinical Surgery*.[3] This book will acquaint both the student and practicing physician with the physical signs of disease which not only are described in detail but also are well documented by a wealth of illustrations, many in color. From a consideration of fundamental states and basic physical signs, the book progresses to include the organ systems and all portions of the body which are reported upon in minute detail along with procedures for demonstrating or eliciting physical signs. Laboratory and other diagnostic adjuncts are occasionally referred to, but a careful physical examination is always considered more important than a laboratory evaluation. Objectivity is stressed, and the physician is taught to rely upon what he can see, feel, and sense. Not only are the common disease and abnormal physical states for a particular geographic area covered but consideration is also given to the uncommon so that the book has a worldwide usefulness.

The completeness of the text material and accompanying illustrations and wide acceptance of the volume are attested to by the fact that this volume is now in its thirteenth edition. There are 868 pages, exclusive of a comprehensive index.

This volume will serve the student in physical diagnosis well and will be equally appreciated and valued by the practicing physician for its excellent and thorough coverage of physical signs useful in clinical surgery.

—*W. Harrison Mehn.*

THE BOOK entitled *Modern Trends in Diagnostic Radiology*,[4] is aptly named. Much of it concerns the direction that clinical diagnostic radiology is taking rather than being merely a digest of material appearing since the second series published in 1953.

The list of contributors is indeed an imposing one, reading like a partial list of "Who's Who in Radiology." The writers are mostly British, a few are Norwegian and Swedish, and there is one lone American, Frederic N. Silverman. The 22 chapters cover as many facets of diagnostic radiology. Some of the material particularly in the chapters on "Evaluation of

[1] TRAUMA IN THE AGED. Edited by Edgar M. Bick, M.D. Introduction by Robert H. Kennedy, M.D. 524 pages, illustrated. $16.00. New York: McGraw-Hill Book Co., Inc., 1960.

[2] SELECTED PAPERS. By Sir Geoffrey Jefferson. 562 pages, illustrated. $22.00. Springfield, Ill.: Charles C Thomas, 1960.

[3] DEMONSTRATIONS OF PHYSICAL SIGNS IN CLINICAL SURGERY, 13th ed. By Hamilton Bailey, F.R.C.S. (Eng.), F.A.C.S., F.R.S.E. 927 pages, 1142 illustrations. $14.50. Baltimore: The Williams & Wilkins Co., 1960.

[4] MODERN TRENDS IN DIAGNOSTIC RADIOLOGY. 3rd series. Edited by J. W. McLaren, M.A., M.R.C.P., F.F.R., D.M.R.E. 274 pages, 209 illustrations. $16.00. New York: Paul B. Hoeber, Inc., 1960.

Cardiac Function by Angiocardiography and Cineradiography," "Radiology in Research," and "Oesophagus" appears to have little routine clinical application. Other material is extremely cogent to the problems of everyday routine radiology. The chapter on "Cerebral Angiography" contains not only a fine description of the technical aspects and interpretation but, in addition, an excellent atlas of roentgenograms. The same can be said about the chapter on "Percutaneous Splenoportography." Silverman's contribution on "Paediatric Radiology" has multiple virtues: the subject material is broad in scope but concisely put and easily read; the roentgenographic reproductions obviously have been carefully selected to illustrate the text to best advantage; and the bibliography is replete with recent review references. The chapter on "Rare Diseases of Bone" would delight the radiologist who treasures every morsel of the unusual, sometimes at the expense of familiarity with the commonplace. This radiologic museum-on-paper is certainly worth visiting. The chapter on "Radiological Contrast Media" is welcomed mainly because of the chart it contains which lists the generic names of the contrast media as well as their registered names. The multiple trade names for a particular medium in the United States, Britain, and the Continent have long been a source of confusion in the roentgenologic literature. At last one can tell which contrast medium is which.

Other chapters in the book certainly also merit careful reading. Still other chapters can be thumbed through or ignored to conserve valuable reading time, especially: "Dental Radiology," and "General Indications for Peripheral Angiography." I wonder about some of the statements made in this apparently authoritative work, for example: McClaren recommending sight developing for soft tissue radiography, Hodson suggesting that the thickness of the kidney can be determined from oblique views, and Grainger remarking that cholecystographic media may further liver damage.

The book contains many excellent roentgenographic reproductions, some in negative and others in positive form. "Bleeding off" of the illustrations has permitted larger and more illustrations per page, a style which publishers would probably do well to adopt. Yet, the chapter on "Hypertension of Renal Origin" does not contain any roentgenographic reproductions whatsoever. Certainly, these would have furthered the understanding of the text.

With the exception of a few chapters, the book will probably not appeal to nonradiologists and trainees in radiology. The radiologist will find the material for the most part interesting, informative, stimulating, and challenging. This book is commendable and recommendable. —*Bertram Levin.*

TO MOST OF US the name of Paré suggests the picture of a young surgeon, anxious and sleepless because he did not have sufficient boiling oil with which to treat his patients' wounds, and fearful that this omission had jeopardized their recovery. The end of the story is well known, and one cannot help recall the picture of a distinguished fellow countryman who several hundred years later spent a sleepless night awaiting the outcome of his experimental inoculation with a virulent culture of anthrax bacilli of sheep which had been vaccinated against anthrax with the attenuated cultures he had prepared.

In translating a number of Paré's case reports and autopsy records,[5] Hamby has given us some graphic glimpses of the life and times of this thoughtful and capable surgeon, and of the difficulties and almost insuperable handicaps that confronted the physician and surgeon of the sixteenth century.

A few direct quotations emphasize the seriousness of the cases Paré describes, of the almost incredible conditions under which wounded patients were sometimes cared for, and of Paré's kindly interest in and solicitude for humble as well as great.

Lance injury, page 27: ". . . one must not omit the terrible wound received by M. Francois de Lorraine, duc de Guise . . . before Boulogne from the stroke of a lance. This entered under the right eye, declined toward the nose and came out the other side between the ear and the neck, with such violence the head of the lance was broken off with part of the shaft and remained in place. It could be withdrawn only with great force, using blacksmith's tongs. Despite this great violence by the blow of the lance that fractured bone, nerves, veins, arteries and other structures being torn and shattered; thanks to God, the duc recovered."

Amputation through elbow joint, page 74: "A poor soldier was shot with an harquebus in the left arm near the wrist and the joint of the hand. The ball lacerated and broke several bones, tendons and other nervous parts. Gangrene developed, then mortification spread nearly to the elbow. Gangrene extended to the shoulder and great inflammation and early gangrene extended to part of the thorax. . . . Because the soldier had been abandoned by several Surgeons I was implored by several of his friends to visit him. After I had seen the mortification, I was encouraged to remove his arm at the elbow. I did this as rapidly as I could, removing the arm without a saw since the mortification was just beyond the elbow, commencing the amputation by cutting the ligaments joining the bones. . . . My incision made, a great flow of blood followed in spite of the tourniquet. I let enough flow to drain and disgorge the part. . . . Then I arrested the blood with the actual cautery, not knowing at the time any other way to accomplish it. This done I loosened the tourniquet gently and made several deep wide incisions in the gangrenous area, avoiding the inner part of the arm because of the great veins, arteries and multitude of nerves that are there. Then I applied the cautery to some of the incisions . . . and then applied the dressing. . . . Fifteen days later the poor soldier developed a convulsion which I had foretold, because of the cold, since he was poorly housed in a granary where he had only a little cover and was exposed to the wind, without fire and other necessities of human existence. Seeing him in such spasm and contraction of the extremities, the teeth clenched and all the lines of the face drawn and tense, as if he wished

[5]THE CASE REPORTS AND AUTOPSY REPORTS OF AMBROISE PARÉ. Compiled and edited by Wallace B. Hamby, M.D., F.A.C.S. Translated from J. P. Malgaigne's "Oeuvres Completes d'Ambroise Paré" Paris 1840. 191 pages. $6.50. Springfield, Ill.: Charles C Thomas, 1960.

to laugh the Sardonic grin, aroused my pity. Desiring to follow the precepts of my Art, not knowing what else to do, I had them put him in a stable in which was a great number of beasts and a great quantity of manure. Then I managed to have fire in two braziers, near which we rubbed his neck, arms and legs. . . . After wrapping the patient in a warm sheet we put him into the manure in a bed of straw with which we covered him, then covered him with the manure, where he remained three days and nights without arising. Then he had a little bowel movement and a great sweat and began to open his mouth a little. Little by little we aided him with instruments put between his teeth. After opening the mouth with this instrument, I inserted a little wooden rod to keep the mouth open. Since he could not chew, I had them give him milk and egg yolks. By these means were the convulsions cured.

"Then followed the cure of the arm, repeating the application of the cautery on the tip of the bone to consume and dry the foreign humors. . . . I also poulticed the affected part to dry and restore it, which poultices were made with a dry, astringent wine in which were boiled red roses, absinthe, sage, laurel, flowers of camomile and melilot, anise and other remedies. By such means the poor soldier was healed."

Treatment of army servant in ambulance, page 168: "One of the servants of a Captain assigned to the Company of M. de Rohan went with others intending to enter a church where the peasants had retreated, thinking to find food by love or by force. But among others, he was well beaten and returned with seven sword cuts on the head, the least penetrating to the second table of the skull. He had four others in the arms and one on the right shoulder which cut more than half the shoulder blade, or scapula. He was brought to the lodge of his Master, who seeing him so wounded, and since we had to leave at daybreak tomorrow, thinking he could never recover, had a grave made and would have thrown him into it, saying that was better than have the peasants massacre and kill him.

"Moved by pity I told him he still might recover if he was dressed well. Many Gentlemen of the Company begged him to have him brought with the baggage, since I had thus volunteered to treat him. This he granted and after I dressed him, he was put well covered and accommodated on a bed in a cart drawn by one horse. I did him the services of Physician, Apothecary, Surgeon and cook. I treated him to the end of his cure and God healed him. All those of three Companies praised this cure. At the first muster that was made the men-at-arms of M. de Rohan's Company each gave me a crown and the archers a half-crown."

There are many more case reports which are of equal interest, and we are indebted to Hamby for making available in interesting and readable form these concise records of a surgeon whose name remains high in the annals of our profession.

—*Sumner L. Koch.*

THOSE WHO HAVE HEARD Benjamin Felson speak will readily recognize his easy style and uncluttered presentation of practical information in *Fundamentals of Chest Roentgenology*.[6] He believes that the routine posteroanterior chest roentgenogram is only a "scout film," and outlines the role of the many other views, positions, and techniques which may be of diagnostic help, with the indications for their use. The "lost art" of chest fluoroscopy is discussed in some detail.

The major part of the book presents practical points in the localization of abnormal shadows, determination of the structures involved, and the nature of the pathologic process depicted on the x-ray film. Certain special roentgen signs are evaluated in the light of the author's personal experience.

This book is not intended to be a treatise on chest roentgenography, but only an outline of chest film interpretation. Emphasis is placed upon utilizing fundamental concepts to arrive at a correct interpretation rather than attempting to recognize specific disease entities based upon past experience. It is highly recommended to all who have occasion to view chest roentgenograms, and should be a frequently consulted "old friend" by those whose major interest is in this field.

—*Robert Fox.*

THE DIAGNOSTIC and therapeutic problems posed by ordinary back pains have not been wholly eradicated by the removal of more intervertebral discs or by bigger and better fusions, and yet most neurosurgeons and orthopedists seem to be thinking only in these terms. Two books published in 1960 buck this trend: *Back Pain; Diagnosis and Treatment Using Manipulative Techniques* by Meanell, and the subject of this review, *Wirbelgelenk und Bandscheibe*[7] by Zukschwerdt, Emminger, Biedermann, and Zettel. Both deserve careful reading and digestion, and while they may fail to convince the reader of the validity of their doctrines, they cannot help but provoke a more critical attitude toward some commonly accepted "truths" regarding back pain. The outstanding feature of *Wirbelgelenk und Bandscheibe* is the initial section on the pathologic anatomy of the vertebral joints with special reference to the facet joints. A knowledge of German is not required to appreciate and comprehend the beautiful illustrations of dissections of the spine. The succeeding discussions of diagnosis and therapy are firmly grounded on their anatomic and pathologic studies. Several unusual and intriguing concepts regarding the pathogenesis of various types of back pain are presented. The discussion of the manipulative treatment of back pain is of greater historical than practical interest. The material in this book will stimulate the reader to look at his patient with an eye keyed to the detection of subtle changes. It is from the observation of patients that the validity of the authors' concepts will be established, or fail.

—*Leonard Peltier.*

FROM THE DAYS of Ramazzini, the father of industrial medicine, there have been so many changes in in-

[6] FUNDAMENTALS OF CHEST ROENTGENOLOGY. By Benjamin Felson, M.D. 301 pages, 450 illustrations. $10.00. Philadelphia and London: W. B. Saunders Co., 1960.

[7] WIRBELGELENK UND BANDSCHEIBE; IHRE BEZIEHUNG ZUM VERTEBRAGENEN SCHMERZ ZUGLEICH EINE STELLUNGNAHME ZUR CHIROPRAKTIK UND BEGUTACHTUNG. By Prof. Dr. L. Zukschwerdt, Dr. med. habil. E. Emminger, Dr. F. Biedermann, and Dr. H. Zettel. 2nd ed. 319 pages, 160 illustrations. Stuttgart: Hippokrates-Verlag, 1960.

dustrial practice that it is difficult even for those devoted to such work to acquire necessary knowledge and maintain pace with the rapidity of industrial growth. The authors' purpose in compiling the volume *Occupational Diseases and Industrial Medicine*[8] was to present essential information for those interested in industrial medicine. An important concept covered throughout the entire publication is that the worker-patient can no longer be considered on the basis of 8 hours a day because many of his problems exist throughout the entire 24 hour period.

The physician being introduced to industrial medicine will appreciate the portions which are devoted to the scope of industrial medicine, organization and function of the occupational health team, coverage of compensation and insurance problems, and rehabilitation and replacement of the involved worker-patient. Chapters are devoted to prevention, recognition, and treatment of those who work with and come in contact with numerous substances such as noxious gases, hydrocarbons, metals and metalloids, resins, plastics, pesticides, propellants, fuels, and other physical and chemical agents. There is also excellent consideration of pneumoconiosis. The chapter devoted to the problem of occupational cancers will be of value to many. The up-to-dateness of the book is illustrated by the inclusion of a section on ionizing radiations. There is an excellent glossary of industrial terms and a table of threshold limit values which will be of value. This is not a book dealing with industrial trauma and only an occasional reference is made thereto.

—W. Harrison Mehr.

[8] OCCUPATIONAL DISEASES AND INDUSTRIAL MEDICINE. By Rutherford T. Johnstone, M.D., and Seward E. Miller, M.D. 482 pages, illustrated. $12.00. Philadelphia: W. B. Saunders Co., 1960.

BOOKS RECEIVED

BOOKS received are acknowledged in this department, and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS. Instructional Course Lectures. Edited by Fred C. Reynolds, M.D. Vol. XXVII. 406 pages, 358 illustrations. $18.50. St. Louis: The C. V. Mosby Co., 1960.

HOSPITAL INFECTION; CAUSES AND PREVENTION. By R. E. O. Williams, M.D., M.R.C.P., R. Blowers, M.D., L. P. Garrod, M.D., F.R.C.P. and R. A. Shooter, M.D. 299 pages, 12 illustrations. $7.50. Chicago: Year Book Publishers, Inc., 1960.

THE JOHNSON RECORDING OSCILLOMETER. By Carl A. Johnson, M.S., M.D. 112 pages, 71 illustrations. $5.00. New York: Pergamon Press, 1959.

NEUROVASCULAR COMPRESSION SYNDROMES OF THE SHOULDER GIRDLE. By Louis M. Rosati, M.D., and Jere W. Lord, M.D. 164 pages, 27 illustrations. $7.25. New York and London: Grune & Stratton, 1960.

CONGENITAL MALFORMATIONS OF THE HEART. Vol. II: SPECIFIC MALFORMATIONS. By Helen B. Taussig, M.D. 2nd ed. 1020 pages, illustrated. $17.50. Cambridge: Harvard University Press, 1961.

RADIATION PROTECTION AND DENTISTRY. By Arthur H. Wuehrmann, D.M.D. 225 pages, 48 illustrations. $6.50. St. Louis: The C. V. Mosby Co., 1960.

CLEFT LIP AND PALATE REHABILITATION. By William H. Olin, D.D.S., M.S., and Duane C. Spriestersbach, Ph.D. 190 pages, 85 illustrations. $9.00. Springfield, Ill.: Charles C Thomas, 1960.

THE CHOICE OF A MEDICAL CAREER—ESSAYS ON THE FIELDS OF MEDICINE. Edited by Joseph Garland, M.D., Sc.D. (Hon.), and Joseph Stokes, III, M.D. 231 pages, no illustrations. $5.00. Philadelphia: J. B. Lippincott Co., 1961.

TEXTBOOK OF MEDICAL PHYSIOLOGY. By Arthur C. Guyton, M.D. 2nd ed. 1154 pages, 774 illustrations. $15.50. Philadelphia and London: W. B. Saunders Co., 1961.

CLINICAL USE OF RADIOISOTOPES. Edited by Theodore Fields, M.S., F.A.C.R.(Assoc.), and Lindon Seed, M.D. 2nd ed. 462 pages, 77 illustrations. $10.50. Chicago, Ill.: The Year Book Publishers, Inc., 1961.

GOOD ENGLISH FOR MEDICAL WRITERS. By Ffrangcon Roberts, M.A., M.D., F.F.R. 173 pages, no illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1960.

MANUAL OF HUMAN DISSECTION. Edited by Charles E. Tobin, Ph.D. 4th ed. 242 pages, 97 illustrations, $7.50. New York: McGraw-Hill Book Co., Inc., 1961.

PRATIQUE OBSTÉTRICALE. By B. Jamain. 3rd ed. 250 pages, no illustrations. 20 NF. Paris: Expansion Scientifique Francaise, 1960.

MODERN TRENDS IN CARDIAC SURGERY. Edited by H. R. S. Harley, M.S., F.R.C.S. 282 pages, 79 illustrations. $15.00. New York: Paul B. Hoeber, Inc., 1960.

SURGICAL DISEASES OF THE CHEST. Edited by Brian Blades, M.D. 571 pages, 267 illustrations. $22.00. St. Louis: The C. V. Mosby Co.: 1961.

ANAESTHETIC ACCIDENTS. By V. Keating, M.B., B.Ch., D.A., F.F.A.R.C.S. 2nd ed.: 282 pages, 14 illustrations. $5.50. Chicago: The Year Book Publishers, Inc., 1961.

SURGICAL UROLOGY. By R. H. Flocks, M.D., and David Culp, M.D. 2nd ed. 430 pages, 126 illustrations. $10.50. Chicago: The Year Book Publishers, Inc., 1961.

NEW AND NONOFFICIAL DRUGS: 1961. Evaluated by the A.M.A. Council on Drugs. 827 pages, no illustrations. $4.00. Philadelphia: J. B. Lippincott Co., 1961.

MODERN TRENDS IN UROLOGY (Second Series). Edited by Sir Eric Riches, M.C., M.S., F.R.C.S. 287 pages, 123 illustrations. $16.00. New York: Paul B. Hoeber, Inc., 1960.

HENRY STANLEY PLUMMER; A DIVERSIFIED GENIUS. By Frederick A. Willius, M.D., M.S.(Med.). 70 pages, illustrated. $4.50. Springfield, Ill.: Charles C Thomas, 1961.

MEDICAL-SURGICAL NURSING. By Kathleen Newton Shafer, R.N., M.A., Janet R. Sawyer, R.N., A.M., Audry M. McCluskey, R.N., M.A., and Edna Lifgren Beck, R.N., M.A. 2nd ed. 832 pages, 141 illustrations. $8.75. St. Louis: The C. V. Mosby Co., 1961.

PARKINSONISM; ITS MEDICAL AND SURGICAL THERAPY. By Irving S. Cooper, M.D., Ph.D., F.A.C.S. 228 pages, 111 illustrations. $16.50. Springfield, Ill.: Charles C Thomas, 1961.

THE SURGICAL TREATMENT OF INTRACRANIAL MENINGIOMAS. By Collin S. MacCarty, B.A., M.D., M.S. 69 pages, 15 illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1961.